Leibniz Gemeinschaft

Der Senat

21. November 2023

Stellungnahme zum Leibniz-Institut für umweltmedizinische Forschung, Düsseldorf (IUF)

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Vorbemerkung

Die Einrichtungen der Forschung und der wissenschaftlichen Infrastruktur, die sich in der Leibniz-Gemeinschaft zusammengeschlossen haben, werden von Bund und Ländern wegen ihrer überregionalen Bedeutung und eines gesamtstaatlichen wissenschaftspolitischen Interesses gemeinsam außerhalb einer Hochschule gefördert. Turnusmäßig, spätestens alle sieben Jahre, überprüfen Bund und Länder, ob die Voraussetzungen für die gemeinsame Förderung einer Leibniz-Einrichtung noch erfüllt sind.[1]

Die wesentliche Grundlage für die Überprüfung in der Gemeinsamen Wissenschaftskonferenz ist regelmäßig eine unabhängige Evaluierung durch den Senat der Leibniz-Gemeinschaft. Die Stellungnahmen des Senats bereitet der Senatsausschuss Evaluierung vor. Für die Bewertung einer Einrichtung setzt der Ausschuss Bewertungsgruppen mit unabhängigen, fachlich einschlägigen Sachverständigen ein.

Vor diesem Hintergrund besuchte eine Bewertungsgruppe am 6. und 7. Februar 2023 das IUF in Düsseldorf. Ihr stand eine vom IUF erstellte Evaluierungsunterlage zur Verfügung. Die wesentlichen Aussagen dieser Unterlage sind in der Darstellung (Anlage A dieser Stellungnahme) zusammengefasst. Die Bewertungsgruppe erstellte im Anschluss an den Besuch den Bewertungsbericht (Anlage B). Das IUF nahm dazu Stellung (Anlage C). Der Senat der Leibniz-Gemeinschaft verabschiedete am 21. November 2023 auf dieser Grundlage die vorliegende Stellungnahme. Der Senat dankt den Mitgliedern der Bewertungsgruppe und des Senatsausschusses Evaluierung für ihre Arbeit.

1. Beurteilung und Empfehlungen

Der Senat schließt sich den Beurteilungen und Empfehlungen der Bewertungsgruppe an.

Das Leibniz-Institut für umweltmedizinische Forschung (IUF) untersucht den Einfluss von Umweltfaktoren auf den menschlichen Körper. Es konzentriert sich dabei auf die Wirkung individueller Umweltstressoren auf die drei Organe Lunge, Haut und zentrales Nervensystem. Zur Untersuchung dieser Organe hält es immunologische, toxikologische sowie epidemiologische Expertise vor.

Die Forschung des IUF ist innovativ und bewegt sich auf hohem Niveau. Ein erfreulich hoher Anteil der Arbeiten (zuletzt 87 %) wird in qualitätsgesicherter Form im Open Access veröffentlicht. Es entstehen teils herausragende Transferergebnisse, vor allem im Bereich neurotoxikologischer Alternativmethoden zu Tierversuchen. Seit 2020 werden sie über die Plattform *Leibniz Alternatives* angeboten. Vor Kurzem wurde auf Basis eines Testkits für die tierversuchsfreie Prüfung toxikologisch wirksamer Substanzen ein Unternehmen ausgegründet. Außerdem berät das Institut Regulierungsbehörden. Seine zentralen Infrastrukturangebote bestehen in bedeutenden epidemiologischen Kohorten. Unter anderem betreibt es gemeinsam mit einer benachbarten Leibniz-Einrichtung, dem Deutschen Diabetes-Zentrum (DDZ), ein Studienzentrum der von Bund und Ländern geförderten NAKO-Gesundheitsstudie. Diese **Ergebnisse** in Forschung, Transfer und

[1] Ausführungsvereinbarung zum GWK-Abkommen über die gemeinsame Förderung der Mitgliedseinrichtungen der Wissenschaftsgemeinschaft Gottfried Wilhelm Leibniz e. V.

Infrastrukturen werden in sieben Arbeitsgruppen und einer Core Unit erarbeitet, von denen drei als „exzellent“, zwei als „sehr gut bis exzellent“ und drei als „sehr gut“ bewertet werden. Der Aufbau einer weiteren erfolgversprechenden Core Unit, die 2020 mittels einer erhöhten institutionellen Bund-Länder-Förderung gegründet wurde, muss nun zügig abgeschlossen werden.

Das IUF hat sein **Gesamtkonzept** seit der vergangenen Evaluierung vor allem durch eine stärkere Fokussierung auf ausgewählte Organe sinnvoll geschärft. Dass das Hauptaugenmerk individuellen Umweltstressoren gilt, ist auch mit Blick auf die begrenzten Ressourcen des Instituts überzeugend. Dies sollte beibehalten und zur weiteren Profilierung des IUF genutzt werden.

Die Gruppen und Core Units bearbeiten gemeinsam derzeit vier **‚Forschungsfelder‘**. Es ist gut nachvollziehbar, dass drei dieser Felder sich auf je ein Organ konzentrieren (Lunge, Haut, zentrales Nervensystem). Das vierte Feld befasst sich im Unterschied dazu mit Störungen des Immunsystems. Im Kontext des derzeitigen Aufbaus der Forschungsfelder bleibt seine Funktion unscharf. Das IUF muss daher klären, wie es den Zugang über Organe und Methoden in seiner internen Organisationsstruktur abbilden möchte und welche Folgen dies für Zuschnitt und Funktionsweise der gruppenübergreifenden Arbeit hat.

Seit seiner Gründung arbeitet das IUF eng mit der Universität Düsseldorf und der dortigen Medizinischen Fakultät zusammen. Mit ihr sind der Wissenschaftliche Geschäftsführer (W3), der das Institut seit über zwanzig Jahren erfolgreich führt, und eine weitere Arbeitsgruppenleiterin (W2) gemeinsam berufen. Nachdem seit der vergangenen Evaluierung zwei W2-Professuren mit dieser Fakultät entfallen sind, wurden zwei Berufungsverfahren mit den Universitäten Bochum und Dortmund für W1-Positionen mit *tenure track* in Bioinformatik und Biostatistik aufgenommen; eines dieser Verfahren ist inzwischen abgeschlossen. Institutionelle Verbindungen in der Region bestehen außerdem zum LIMES-Institut an der Universität Bonn und zum DDZ. Nun stehen zwei weitere **gemeinsame Berufungen** an: Spätestens 2026 ist die wissenschaftliche Leitung des IUF neu zu besetzen. Bereits zuvor erreicht die Leiterin der für die Immunologie zentralen Arbeitsgruppe die Altersgrenze. Ihre Nachfolge sollte unter Beteiligung der neuen Geschäftsführung als Professur besetzt werden. Bei den anstehenden Berufungen sollte das strategische Zusammenspiel des IUF mit den kooperierenden Hochschulen gut in den Blick genommen werden. Der Senat bittet den Aufsichtsrat, bis zum 15. Dezember 2024 zu den Planungen für die gemeinsamen Berufungen zu berichten.

Das **wissenschaftliche Personal** findet am IUF gute Bedingungen für die eigene Weiterqualifikation vor. Schon seit 2011 gibt es ein sehr gutes strukturiertes Promotionsprogramm. Mit der Beteiligung an zwei DFG-Graduiertenkollegs seit 2021 und der geplanten Erhöhung der Zahl gemeinsamer Berufungen steht zu erwarten, dass die zuletzt abgesunkenen Promotions- und Promovierendenzahlen künftig wieder steigen. Das Institut sollte außerdem auf einen intensiveren personellen Austausch mit anderen Einrichtungen im In- und Ausland hinwirken. Das gilt insbesondere für die Rekrutierung wissenschaftlichen Personals und die Förderung von Wissenschaftlerinnen und Wissenschaftlern in der Qualifikationsphase. Es ist erfreulich, dass der Anteil von Frauen am wissenschaftlichen Personal über 60 % beträgt und auf den Leitungspositionen ausgewogen ist.

Bereits bei den beiden vergangenen Evaluierungen 2007 und 2015 wurde die Unterbringung des IUF als prekär eingeschätzt. Nach langer Verzögerung wird ab dem kommenden Jahr ein **Neubau** für das Institut einschließlich der Tierhaltung errichtet, der 2027 übergeben werden soll. Die institutionelle **Förderung** ist auskömmlich. Etwa ein Viertel seines Budgets für laufende Maßnahmen wirbt das IUF durch Drittmittel ein. Jüngere Erfolge bei der Einwerbung von DFG-Mitteln begründen die Erwartung, dass dieses Niveau in den nächsten Jahren mindestens gehalten werden kann.

Die Sicherung guter wissenschaftlicher Praxis hat am IUF einen hohen Stellenwert. Zur Weiterentwicklung der **Qualitätssicherung** wird empfohlen, ein elektronisches Laborbuchsystem einzuführen. Für die Auswahl eines geeigneten Modells bietet sich ein Erfahrungsaustausch mit Leibniz-Einrichtungen an, die solche Systeme bereits nutzen. Es sollte sichergestellt werden, dass die Mitglieder des Wissenschaftlichen Beirats künftig spätestens nach zwei Amtszeiten ausscheiden und die Altersstruktur im Gremium ausgewogen ist.

2. Zur Stellungnahme des IUF

Der Senat geht davon aus, dass das IUF die Empfehlungen und Hinweise aus dem Bewertungsbericht bei seiner weiteren Arbeit berücksichtigt.

3. Förderempfehlung

Der Senat der Leibniz-Gemeinschaft empfiehlt Bund und Ländern, das IUF als Einrichtung der Forschung und der wissenschaftlichen Infrastruktur auf der Grundlage der Ausführungsvereinbarung WGL weiter zu fördern.

16 January 2023

Annex A: Status report

Leibniz Research Institute for Environmental Medicine, Düsseldorf (IUF)

Contents

1. Key data, structure and tasks

Key data

Year established:	2001
Admission to joint funding by Federal and *Länder* Governments:	2011
Admission to the Leibniz Association:	2011
Last statement by the Leibniz Senate:	2016
Legal form:	non-profit, limited liability company (gGmbH)
Responsible department at *Länder* level:	Ministry of Culture and Science of the State of North Rhine-Westphalia (MKW)
Responsible department at Federal level:	Federal Ministry of Education and Research (BMBF)

Total budget (2022)

€ 8.4m institutional funding

€ 3.2m revenue from project grants

Number of staff (2022)

52 individuals "research and scientific services"

34 individuals "science supporting staff (laboratories, technical support etc.)"

13 individuals "science supporting staff (administration)"

Mission and structure

Statutory mission

"The objective of the company is to promote science and research through studies in environmental medicine, especially in currently relevant subject areas in the fields of epidemiology, toxicology, immunology, and cell biology, and including molecular ageing research and risk assessment with respect to human health."

Organisation

The IUF is headed by a Scientific Manager and a Legal-financial Manager. Research at the IUF is carried out in four research fields (RF) which study environmentally-induced ageing in four major organ systems:

- the pulmonary system (RF1)
- the skin (RF2)
- the central nervous system (RF3)
- the immune system (RF4)

The essential organizational units that contribute to these four research fields are

- 7 working groups (WG)
- 2 liaison groups, i. e. collaborating university-based groups (LG)
- 2 core units
- a public-private partnership platform, "Leibniz Alternatives"

Each of them is headed by a senior scientist. From 2023 onwards, two junior research groups (JRG) will be established.

2. Overall concept and core results

The research mission of the IUF is the molecular prevention of environmentally-induced ageing and associated diseases. The institute develops models for risk assessment and for identifying strategies for prevention and intervention. With regard to knowledge and technology transfer, the IUF advises regulatory authorities and cooperates with industry. It also operates research infrastructure, by maintaining the SALIA cohort and by, together with the fellow Leibniz institute DDZ – German Diabetes Centre, running a German National Cohort (NAKO) recruitment centre.

The IUF focuses on a combination of physical and chemical environmental stressors of global relevance including particles, non-ionising radiation, and selected chemicals (which, taken together, it calls the 'environmental exposome'). It combines environmental epidemiology, molecular toxicology, molecular ageing research, and immunology, and studies how the stressors affect the lung (RF1), the skin (RF2), the central nervous (RF3) and immune systems (RF4).

The four RF address three common research topics: (i) interorgan crosstalk in environmentally-induced ageing, (ii) the identification and characterization of susceptible groups, and (iii) the analysis of environmentally-relevant exposomal factors. The IUF also (iv) develops alternative methods to animal testing. This research contributes to (v) improving risk assessment and developing novel preventive measures.

Results

The IUF was asked to identify up to ten of its most important results in the fields of research, research infrastructures, and knowledge and technology transfer since the last evaluation. It pointed out the following research achievements:

(i) Interorgan Crosstalk

- It was found that traffic-related particulate matter (TRPM) exposure is linked to Alzheimer's disease, and that the lung has an important role in mediating this effect. (RF1, RF3)

(i) Interorgan Crosstalk and (v) Preventive Measures

- It was shown that all skin cell populations express the AHR, and that AHR signalling is important for skin health and disease. Findings during the reporting period include that the AHR represses DNA repair in UVB-irradiated keratinocytes and

thus contributes to skin photocarcinogenesis in mice, and that a modulation of AHR activity via the gut affects skin barrier function and the composition of the skin microbiome. (RF2, RF4)

(ii) Susceptible Groups

- It was observed that improved air quality benefits lung function in elderly, and that this effect is modulated by genetic polymorphisms. (RF1)
- It was found that the aldo-keto reductase (AKR)1C3, which may impair epidermal barrier function by shaping cutaneous prostaglandin D2 metabolism, is upregulated in polycyclic aromatic hydrocarbon and airborne particulate matter-exposed keratinocytes and human *ex vivo* skin. In a German birth cohort, carriers of a gain-of-function polymorphism in the AKR1C3 gene were identified to be susceptible towards airborne particulate matter-triggered atopic dermatitis. (RF2, RF4)
- It was found that eczema in the elderly is associated with exposure to traffic-related air pollution and is non-atopic in nature. (RF4)
- It was shown that pollutants such as traffic-related nanoparticles corrupt resilience pathways of ageing in the model organism *C. elegans* and shift age-related degenerative processes such as neurodegeneration and neuromuscular defects from middle-aged worms to young worms, which thus transform prematurely into a vulnerable group. (RF3)

(iii) Exposomics

- It was discovered that traffic-related air pollution increases pigmentation of human skin by inducing melanin de novo synthesis. (RF2)

(iv) Alternative test methods

- Stem cell-based test methods for developmental neurotoxicity evaluation were set up as parts of the EFSA/OECD *in vitro* test battery. They cover six of eight neurodevelopmental processes of the whole international battery. (RF3)
- The developing oligodendrocyte was identified as a specifically susceptible cell type during human brain development. (RF3)

(v) Preventive Measures

- Novel biological functions of DNA repair enzymes such as CSB, CSA, and XPA were discovered. Besides DNA repair, these enzymes regulate epigenetic and metabolic processes. Targeting these functions prevents e.g. clinical manifestation of the CSB syndrome. (RF2)

The IUF published an annual average of 76 articles and papers in 2020–2022, almost invariably in peer-reviewed journals. On average, it filed one application giving rise to a right of property each year, and it holds two property rights (as of 31/12/2022).

3. Changes and planning

Development since the previous evaluation

Since the IUF was last evaluated in 2016, its research strategy remained by and large unchanged. It implemented the following organisational changes:

- Three working groups were discontinued for various reasons in 2016–2019. They had a cardiovascular, endocrinological, and epidemiological focus, respectively. One liaison group that worked on chronobiology was also terminated (2018). In turn, in 2016, the two junior research groups to focus on environmental epidemiology and dermatology, respectively, were promoted to become regular working groups. Since the number of regular working groups was reduced to seven, the IUF began to support each of them, in addition to core funding, with at least one postdoc and one technician position.
- Two core units were established. In 2018, a core unit for genome editing, modern sequencing methods and human 3D model development was founded (GEMD). In 2021, another core unit was established (CEA). It focuses on modelling complex exposure scenarios. The federal and state governments increased the institute's institutional funding in order to establish these units.
- Since 2020, the IUF has bundled its activities to develop alternative test methods in a public-private partnership platform, "Leibniz Alternatives". Together with industry partners, it focuses on (developmental) neurotoxicity and recently includes embryo- and immunotoxicity.

Strategic work planning for the coming years

The IUF intends to establish two junior research groups for computational phenomics and biostatistics, respectively. Joint appointment processes for the leaders (W1 professorships with tenure track) have commenced. By building up expertise in these fields, the IUF aims to set the grounds for developing explanatory and predictive models of environmentally-induced ageing and associated diseases.

The scientific manager will retire by 2026 at the latest. The SAB recommends that the replacement process for the scientific manager should begin in early 2024.

Also, the head of the working group "Role of AHR in immuntoxicology", who at present acts as the leader of research field 4, will retire in 2024. The IUF considers jointly appointing a scientist, who recently was awarded a five-year junior research group grant by the *Land* NRW, as a junior professor in order to further the work in research field 4.

The IUF follows a research strategy that defines short-term, mid-term and long-term goals. Short-term goals are defined on an annual basis in the program budget. Like mid-term goals, they are commonly supported by project grants and the IUF's being involved in national and international research alliances. The institute's long-term strategy (2023–2029) will focus on targeted and personalised prevention of environmentally-induced ageing and associated diseases. To this end, it has identified five overarching topics, which will make use of the institute's comprehensive panel of models ranging from monolayer cell cultures to population studies:

- interorgan crosstalk
- susceptible groups
- exposomics
- phenomics
- alternative test methods.

4. Controlling and quality management

Facilities, equipment and funding

The IUF receives institutional funding of 8.6m € on average per year (2020–2022). The institute's third-party revenues totals 2.9m € on average per year (25 % of the total budget). For the major part, third-party funding comes from the following sources:

- DFG: ⌀ 722k € / 25 %
- Federal and *Länder* governments: ⌀ 703k € / 24 %, including ⌀ 149k € for the NAKO study
- EU: ⌀ 536k € / 18 %
- Leibniz Association: ⌀ 306k € / 10 %
- Industry: ⌀ 260k € / 9 %

With the exception of the animal research facility, which is managed by the IUF alone, all facilities are rented from the *Land*'s real estate agency (BLB NRW). According to the IUF, the buildings have reached the end of their useful lifespan. A replacement building on an adjacent site is in planning and expected to be constructed by 2027.

The IUF has outsourced its IT services. It states that all its data is stored on a centrally hosted server with a comprehensive backup system.

Organisational and operational structure

The IUF is a non-profit, limited liability company (*gGmbH*). Its bodies are the meeting of the shareholders, the supervisory board, the scientific advisory board, and the management.

The IUF's executive body, the management (*Geschäftsführung*), consists of at least two members. It is currently composed of a scientific manager (*Wissenschaftlicher Geschäftsführer*) with a renewable five-year contract and a legal-financial manager (*Kaufmännischer Geschäftsführer*) with an unlimited contract, who is the budget officer. They meet several times per week. The scientific manager, in consultation with group leaders and the scientific advisory board, develops the institute's research program.

Working and junior research groups at the IUF are entitled to one postdoc and one technician position each. They receive annual institutional funding of 10k €. Junior research groups are established by the scientific manager upon recommendation of the SAB. Evaluations by the SAB are scheduled after three and six years. Evaluation may lead to terminating or, after six years, to promoting the group to a permanent regular working group.

The management regularly meets with working group leaders, including end-of-the-year and mid-term meetings, in part devoted to strategic discussions and target agreements. The regular monthly meetings with all group leaders, representatives of the service facilities, PhD and postdoc representatives were suspended during the Covid-19 pandemic. Instead, the managers now regularly meet with group leaders individually (and in smaller groups).

Quality Management

The IUF is committed to the Leibniz Association's guidelines for good scientific practice and makes them available via the intranet. Since 2007, the IUF has essentially implemented the Leibniz *Guiding Principles for Our Actions* in its *IUF's Core Values*. Upon starting doctoral studies, PhD students are familiarised by the scientific manager both with these rules and the recommendations of the 'Vancouver Convention'[1]. Two group leaders are elected as ombudspersons.

A company agreement is in place that requires researchers to comprehensively document working steps and archive original data sets. Original and secondary data is obligatorily deposited at the scientific manager's office upon acceptance for publication. Wherever possible and appropriate, scientists are encouraged to make their data available to the public.

German federal law stipulates that all animal experiments be authorised. Therefore, before filing an application, IUF researchers take into account the 3R principles of refining, reducing, and replacing animal testing. This process is accompanied by the animal welfare officer, who is a veterinarian, and by experts in animal husbandry.

The IUF aims for publishing original research in international peer-review journals. It supports open access, and in 2022, 33 of the 38 publications (87 %) with corresponding authors from the IUF were published open access. The IUF has started to use early and prepublication servers such as *bioRxiv*. For inventions that may require protection (patents), the IUF collaborates with an external service provider.

Working and junior research groups' funds are allocated according to performance (PFA/performance-based funding allocation); in 2021, groups received between 3,185 € and 38,459 € (⌀ 12,469 €) in addition to institutional funding (10k €). Parameters are the amount of third-party funding and the impact factor of the journal wherein an article was published; a bonus is granted for joint projects/publications of several groups. The parameters were developed by group leaders and approved by the scientific advisory board.

Quality management by advisory board and supervisory board

The scientific advisory board (SAB) consists of at least six members who are selected to represent the variety of disciplines at the institute. It advises the management and the supervisory board on scientific matters, in particular with regard to the program budget. The SAB meets once a year. In a three-year cycle, it evaluates every research group; usually

[1] http://www.icmje.org/icmje-recommendations.pdf

groups from one research field or working on one overarching topic are jointly evaluated. It also conducts an audit between evaluations.

The supervisory board (SB) is composed of currently six full members and, as a non-voting member, the SAB chairperson. It decides on the general research objectives and on the general administrative affairs of the company. The SB meets twice a year.

5. Human Resources

Leading scientific and administrative positions

For recruiting leading scientific and administrative staff, the IUF follows the standards established by the Leibniz Association. The scientific manager (C4/W3 professorship), who also heads a group, and one group leader (W2 professorship) are jointly appointed with Düsseldorf University (see chapter 6). For recruiting, the IUF and the university establish a joint search committee to identify the most suitable candidate. Adhering to the same regulations, the IUF intends to appoint two (possibly three) tenure-track junior professors jointly with university partners.

For recruiting leading scientific staff who are not appointed jointly with a university partner, the IUF uses recruitment symposia. The committee consists of the IUF management, SAB members, and if appropriate external experts.

Staff with a doctoral degree

Institute-funded postdoc positions are initially filled on a fixed-term basis (usually two years). If requested by the group leader, tenure is granted by the management.

A structured postdoctoral training program is in place since 2015. It includes, among others, funding for one soft-skills course at Düsseldorf University per year, project progress discussions, and internal seminar talks. Postdocs at the IUF are also eligible to apply for funding (max. 1,000 €) for individual career development measures. If aiming for habilitation, they may teach at partner universities.

As a recognised training institute, the IUF offers its employees the opportunity of advanced training as toxicology specialist (i. e., European registered Toxicologist).

Junior researchers at the IUF often accept positions in industry and regulatory authorities. Since 2016, one working group leader and one liaison group leader obtained a habilitation; another one was appointed to a professorship at a German university.

Doctoral Candidates

The IUF introduced a structured PhD program in 2011, wherein students are supervised by a PhD committee. It includes a PhD agreement, an initial meeting with the scientific manager devoted to, among others, matters of good scientific conduct, an introductory presentation to the institute's colloquium within the first six months, and annual written reports to the PhD committee. Shortly before or after the viva voce examination, a final presentation is given. Also, PhD candidates have the opportunity to take at least four soft-

skills courses at collaborating universities. The IUF is a member of Düsseldorf University's interdisciplinary graduate and research academy, iGRAD.

PhD candidates regularly are employed at 65 %, unless stipulated otherwise by third-party funders. Regardless of the availability of third-party funding, the IUF guarantees PhD funding for three full years. On average, completing a PhD degree at the IUF takes around 3.7 years. Between 2020 and 2022, 8 PhD degrees were completed.

Medical doctorates are also completed at the IUF, generally before finishing medical school (2020–2022: 4). Candidates are not supervised by a committee. They are members of the medical research school at Düsseldorf University, medRSD.

PhD candidates and postdoctoral researchers elect usually two representatives who regularly meet with the IUF management. They are linked with the Leibniz Association PhD and Postdoc networks, respectively.

Science supporting staff

The IUF offers three-year vocational apprenticeships in the fields of animal caretaking and, recently, office management. The institute aims to offer its apprentices a one-year follow-up contract after their training is completed. At present, one apprenticeship is in place.

Technical and administrative staff attend professional development training courses on a regular basis. The demand for further qualification is assessed in regular discussions with the legal-financial manager. Scientific and non-scientific staff are offered the opportunity to obtain the FELASA[2] B qualification, which is a further qualification for handling laboratory animals.

Equal opportunities and work-life balance

The IUF is committed to the Leibniz and DFG guidelines for equal opportunities and has implemented the so-called cascade model as envisaged by the federal and state governments. At present, 62 % of its scientific staff are women (32 of 52); among group leaders, the ratio is 57 % (4 of 7).

In 2020, the IUF was re-certified in the berufundfamilie audit. Regulations in place are, among others, flexible working hours and an uncomplicated process to apply for time-off for private reasons. The IUF has introduced working from home which is now regulated in a company agreement; an informal application to the superior is sufficient.

6. Cooperation and environment

Universities

The most important university partners of the IUF are the universities of Düsseldorf, Bochum, Dortmund, and Bonn. Two joint appointments are in place with Düsseldorf University (scientific manager, C4, since 2002; group leader, W2, since 2012). Until 2016 and

[2] Federation of European Laboratory Animal Science Associations.

2019, respectively, two further W2 professors were jointly appointed (one of them a Heisenberg professor, who was funded by the DFG for five years). With the universities of Bochum and Dortmund, joint recruitment processes for a junior professorship with tenure track each have been initiated. A further junior appointment is discussed with Bonn University.

Besides, collaboration with Düsseldorf University includes, among others, one liaison group and cooperation in DFG and Leibniz programmes such as the recently awarded research unit (DFG-FOR 5489) including nine projects of different institutions led by the IUF. With the TU Dortmund IUF collaborates in the research training group (RTG) 2624. IUF scientists serve on university committees and contribute to teaching and student supervision. There is a second liaison group with the LIMES institute at the University of Bonn; the institute head holds a non-remunerated Leibniz Chair at the IUF.

Leibniz Association

The IUF participates in two Leibniz research alliances, Resilient Ageing and Advanced Materials Safety. It coordinates the Leibniz research network Stem Cells and Organoids and is a member of the network Immune-mediated Diseases. The IUF participates in a TROPOS-led project funded under the collaborative excellence scheme of the Leibniz Association.

International Cooperation

The institute's most important international partners are the Dutch National Institute for Public Health and the Environment (RIVM), Fudan University, Shanghai, the Indian Institute of Technology (IIT), Mumbai, and Kanazawa University, Japan. With these institutions and further partners it collaborates in joint projects, cohort studies, and consortia.

Institution's status in the specialist environment

According to the IUF, research in environmental medicine at German universities is largely confined to questions of environmental hygiene. It states that research in analysing the molecular mechanisms involved in environmentally-induced health damage is scarce, and that there are no structured research programs.

On the university level, the IUF identifies the Ulm-based DFG-Collaborative research centre 'Aging at interfaces' as related, but as following a fundamentally different research approach. Among non-university research institutes, it mentions Helmholtz Munich, with which the IUF collaborates in epidemiological studies, and the Helmholtz Centre for Environmental Research, Leipzig, which has a very different focus, although both institutions collaborate in the fields of neurotoxicity and alternative method development. The IUF describes its research as being highly complementary to that pursued at the Leibniz institute FLI in Jena, and it states that the IUF's environmental research focus is not addressed by the Cologne-based excellence cluster on cellular stress responses in ageing-associated diseases, CECAD.

7. Subdivisions of the IUF

Overview of the groups and their participation in the research fields

	Research fields			
	1	**2**	**3**	**4**
WG Esser		o		X
WG Fritsche			X	o
WG Haarmann-Stemmann		X		o
WG Krutmann		X	o	o
WG von Mikecz			X	
WG Schikowski	X	o	o	o
WG Schins	X		X	X
LG Ventura			X	
LG Weighardt				X

X: focus on; o: participation

Research fields

Research field 1: Environmentally-induced pulmonary ageing

[7.7 FTE, of which 2.8 FTE Research and scientific services, 1.8 FTE Doctoral candidates, and 3.1 FTE Supporting staff]

The main task of the RF1 is to investigate the mechanisms by which anthropogenic and natural particles trigger degenerative or ageing processes of the lungs and the impact of further globally relevant environmental factors, such as temperature, on them. Expertise from the fields of toxicology, environmental epidemiology and lung ageing research are combined to study how such exposomal factors can affect respiratory health using approaches that range from *in vitro* cell models and controlled rodent inhalation exposures to investigations in human cohorts. The particulate toxicants that are being investigated include traffic-related fine and nano-size particles, mineral dusts, micro- and nanoplastics, and advanced (nano)materials. Research also addresses the potential contributing effects of the ubiquitous non-particulate, gaseous pollutants in ambient air pollution, i.e. nitrogen dioxide and ozone.

The RF1 explores mechanisms of inter-organ crosstalk and potential translocation pathways of ambient (ultrafine) particles from the respiratory tract to the brain, using both epidemiological and animal experimental approaches. The epidemiological group uses polygenic risk scores and gene-environment interaction approaches to study susceptibility to particle-induced lung diseases, whereas the wet lab research of the RF1 uses advanced human cell-based models in air-liquid-interphase exposure conditions for risk assessment and mechanistic studies with particles.

RF1 contributes to the recently initiated *Leibniz Research Alliance Advanced Materials Safety* (since 2022) which succeeds the former *Leibniz Research Alliance Nanosafety* (2012-2021). Knowledge transfer is ensured through expert and advisory activities of RF1 members.

The research has been shifted from the analysis of two organ systems i.e. pulmonary and cardiovascular, towards the exclusive investigation of the respiratory tract system. Between 2020 and 2022, the RF1 published 18 papers on average per year, mainly in peer-

reviewed journals. Its third-party revenues totalled 253k € on average per year. Third-party funding mostly comes from the DFG (⌀ 110k €), federal and *Länder* governments (⌀ 64k €), the EU (⌀ 45k €), and the Leibniz Association (⌀ 31k €).

Research field 2: Environmentally-induced skin ageing

[11.3 FTE, of which 5.7 FTE Research and scientific services, 1.2 FTE Doctoral candidates, and 4.4 FTE Supporting staff]

In the RF2, mechanisms are studied by which environmental factors, in particular non-ionising radiation and particulate matter, contribute to skin ageing, inflammation, and carcinogenesis. The RF2 combines expertise in ageing research, dermatology, toxicology, immunology, biostatistics, and environmental epidemiology, including computational exposure assessment, 3D (organoid) model development, and genome editing. Major lines of research include

- the analysis of AHR's contribution to UV radiation-induced skin ageing and skin carcinogenesis;
- non-canonical functions of DNA repair enzymes, their impact on UV radiation-induced skin ageing and skin cancer, and their relevance for extracutaneous disease manifestations;
- the pathomechanisms through which airborne particulate matter and commonly associated polycyclic aromatic hydrocarbons induce and/or aggravate inflammatory skin diseases;
- the identification and interactions of exposomal factors (different spectra of solar radiation, air pollution, climatic factors, and chemicals), and the assessment of their relative contribution to ageing-/cancer-associated processes, with a focus on distinct skin ageing phenotypes;
- air pollution-induced skin damage, including (epi)gene–environment interactions in different ethnical groups; and
- the crosstalk of cutaneous and extracutaneous tissue ageing.

Together with industry partners, the RF2 contributes to developing novel measures to prevent skin ageing and associated diseases. It regularly advises medical associations, industry, and consumers about the safety and efficacy of existing protective measures.

Between 2020 and 2022, the RF2 published 28 papers on average per year, mainly in peer-reviewed journals. Its third-party revenues totalled 758k € on average per year. Third-party funding mostly comes from the DFG (⌀ 261k €), federal and *Länder* governments (⌀ 228k €), and the Leibniz Association (⌀ 138k €). The RF2 filed a total of 1.5 patents. Three PhD degrees, two medical doctorates, and one habilitation were completed.

Research field 3: Environmentally-induced disturbances of the central nervous system / neurotoxicity

[20.5 FTE, of which 11.1 FTE Research and scientific services, 3.9 FTE Doctoral candidates, and 5.5 FTE Supporting staff]

The RF3 addresses the overarching topics of susceptible groups and inter-organ crosstalk in the light of neurotoxicity. Emerging global neurotoxicants like endocrine disrupting chemicals and air pollution, including environmental particles, are systematically studied in susceptible groups (i.e. on the developing, the adult, and the aged nervous system). Thereby, specific modes of action for different life stages are identified using stem cell-based *in vitro* methods, the model organism *C. elegans*, and mouse models. This method spectrum is complemented by genome editing, computational bioinformatics tools including artificial intelligence, low- to high-throughput assessment of noxae across different models and taxa, as well as epidemiology. This information is used for hazard identification of noxae due to their disturbance of key characteristics in neurotoxicity. The topic of inter-organ crosstalk is addressed in *C. elegans*, in mice, and in epidemiological studies. Cross-organ consequences of nanomaterial exposure build the center of these studies. The RF3 uses these methods for research in the following fields:

- alternative strategies for developmental, adult, and lifespan neurotoxicity evaluation;
- endocrine disruption-related (developmental) neurotoxicity;
- disease models;
- *in vitro* and *in vivo* investigations of xenobiotic-induced neurodegeneration; and
- life span-resolved, chronic toxicity of nanomaterials.

Technology and knowledge transfer are integral parts of the RF3. A Leibniz Transfer case study for developmental neurotoxicity is conducted.

Between 2020 and 2022, the RF3 published 30 papers on average per year, mainly in peer-reviewed journals. Its third-party revenues totalled 1,461k € on average per year. Third-party funding mostly comes from the EU (⌀ 465k €), federal and *Länder* governments (⌀ 325k €), US and Danish public sector donors (⌀ 212k €), industry (⌀ 151k €), the DFG (⌀ 146k €), and the Leibniz Association (⌀ 138k €). Four PhD degrees, two medical doctorates, and one habilitation were completed.

Research field 4: Environmentally-induced disturbances of the immune system

[9.2 FTE, of which 4.5 FTE Research and scientific services, 1.6 FTE Doctoral candidates, and 3.1 FTE Supporting staff]

Environmental influences on the immune system can manifest either as aberrant activation, leading to allergies, autoimmune disorders, or sterile inflammation, or as immunosuppression with possible consequences such as cancer, barrier impairments, or higher infection rates. The underlying molecular mechanisms are complex and diverse, but chemicals broadly fall into two areas: covalent protein or DNA-adduct formation and non-cova-

lent interference with cellular signalling. The RF4 seeks to identify and analyse such molecular mechanisms and their immunological consequences. Its work draws on modern *in silico*, *in vitro*, and *in vivo* models, some of which were generated specifically at the IUF (for instance gut organoids, genetically modified mice, microbiome and gene expression profiles). As part of the Leibniz Alternatives, models for developmental (neonatal) immunotoxicity testing are developed, using hiPSC-based differentiated immune cells as a first step on the road to regulation.

Genetics and other factors shape the susceptibility against environmental noxae, and also determine the outcome of the immunological response. These factors include, inter alia, ageing, dietary habits, immune experience, and commensal microbiota. This is analysed by the epidemiology group in the RF4, with a focus on ageing processes and the genetic background of populations. Both approaches, molecular research and epidemiology, interconnect and profit from each other. The RF4 strategically focuses on environmental persistent organic pollutants (e.g. dioxins), air pollution, micro- and nano-particles (environmental or synthetic), and UV irradiation. To understand the role of the AHR in the immune system, naturally occurring ligands, in particular dietary compounds and bacterial metabolites, are added.

Between 2020 and 2022, the RF4 published 14 papers on average per year, invariably in peer-reviewed journals. Its third-party revenues totalled 237k € on average per year. Third-party funding mostly comes from the DFG (⌀ 80k €), the Jürgen Manchot foundation (⌀ 75k €), and federal and *Länder* governments (⌀ 68k €). The RF4 filed a total of 0.5 patents. One PhD degree and one medical doctorate were completed.

Working groups

WG Esser: "Role of AHR in immunotoxicology"

[4.7 FTE, of which 3.0 FTE Research and scientific services, 0.7 FTE Doctoral candidates, and 1.0 FTE Supporting staff]

This WG analyses the role of the AHR in immunotoxicology, with a special focus on the barrier organs skin and gut. In particular, the differentiation and function of immune cells in these organs are studied using conditional gene deficient mice and dietary interventions with AHR ligands. AHR is a transcription factor highly expressed in these organs, whose activity is initiated by binding to small molecular weight chemicals that are either present as environmental pollutants (e.g. dioxins), generated endogenously (e.g. the UV-photoproduct FICZ), or taken up by the diet (e.g. glucosinolates from Brassicaceae plants), or that are gut microbial metabolites. AHR signalling is needed for xenobiotic metabolising enzyme induction, and for the expression patterns of many cell-specific genes involved in differentiation and immunity. The WG's research aims at laying the ground for rational therapeutic intervention. The WG demonstrated the critical role of AHR for Langerhans cells and γδT cells in the skin, as well as AHR's importance for the skin barrier, or for oral tolerance. Current studies look at changes in the microbiome for the gut-skin axis as a function of AHR signalling and dietary cues. One project seeks to integrate γδT cells into a human skin model. The WG has generated a number of conditional mouse models, which

are also available for the other WGs at the IUF, and implemented a novel FACS[3]-based method for detecting microbial pattern changes in gut and the skin.

Between 2020 and 2022, this WG published 5 papers on average per year, mainly in peer-reviewed journals; an average three of which were co-authored with other WGs. Its third-party revenues totalled 95k € on average per year. Third-party funding comes from the Wilhelm Sanders Foundation (⌀ 56k €) and from the DFG (⌀ 39k €).

WG Fritsche: "Alternative method development for environmental toxicity testing"

[15.1 FTE, of which 6.8 FTE Research and scientific services, 3.9 FTE Doctoral candidates, and 4.4 FTE Supporting staff]

This WG specialises in the set-up and scientific validation of alternative methods to animal experiments and their use for mode-of-action analyses of substances. The work focuses on developmental and adult neurotoxicity, yet also includes other toxicological endpoints like embryotoxicity and developmental immunotoxicity. The WG set up a species-overarching (human, mouse, rat, rabbit) 3D neurosphere test system for quality-controlled, standardised and largely automated developmental neurotoxicity (DNT) hazard characterisation, which is an integral part of the DNT *in vitro* battery supported by EFSA and the OECD. Artificial intelligence-based cell identification from high content imaging analyses was established. A data base and a biostatistical pipeline were set up for comparative biostatistical data processing. Mechanistic studies of the group feed into the Adverse Outcome Pathway concept, and multiple neurotoxicity AOPs were set up. The DNT work is expanded to endocrine disruption-mediated DNT, and one of the WG's established assays is currently under validation at the French platform PEPPER. WG data also contributes to the novel toxicological concept of 'ontologies' for 'cognitive function defects' with the aim of regulatory application. All these tools together with the recent BrainSphere model for assessing acute neurotoxicity contribute to next generation risk assessment.

Between 2020 and 2022, this WG published 13 papers on average per year, mainly in peer-reviewed journals; an average three of which were co-authored with other WGs. Its third-party revenues totalled 1,115k € on average per year. Third-party funding essentially comes from the EU (⌀ 402k €), federal and *Länder* governments (⌀ 288k €), US and Danish public sector donors (⌀ 212k €), and industry (⌀ 166k €). Two PhD degrees and one medical doctorate were completed.

WG Haarmann-Stemmann: "AHR Signalling & Environmentally-induced skin damaging"

[5.1 FTE, of which 2.0 FTE Research and scientific services, 1.3 FTE Doctoral candidates, and 1.8 FTE Supporting staff]

This WG investigates the biological functions of the AHR signalling pathway in skin exposed to environmental stressors. The main focus of the research is on new functions of

[3] Fluorescence Activated Cell Sorting.

the AHR in the stress response of cutaneous cells, in particular epidermal keratinocytes, exposed to UV radiation and ubiquitous environmental pollutants, such as polycyclic aromatic hydrocarbons and dioxins. The overall aim is to identify novel molecular targets for the development of preventive and therapeutic measures against environmentally induced skin diseases.

The AHR was identified to critically contribute to skin photocarcinogenesis in mice by repressing both nucleotide excision repair and apoptosis in UVB-irradiated keratinocytes. Currently, the potential impact of crosstalk between different exposomal factors on adaptive and maladaptive stress responses in the skin is assessed. In the context of skin ageing and carcinogenesis, the group collaborates with the other dermatological WG to compare the outcome of single UVA and UVB irradiation protocols versus sequential and simultaneous exposure. By combining chemical treatment with UV exposure protocols, it investigates whether a modulation of DNA repair by AHR agonists has an impact on UVB-initiated skin carcinogenesis in mice. It was found that polycyclic aromatic hydrocarbons but not dioxin-like compounds stimulate the expression of aldo-keto reductase (AKR)1C3 and the associated 11-ketoreduction of prostaglandin D2 via a non-canonical AHR signalling pathway. The resulting metabolite, 9,11-prostaglandin F2, may contribute to the worsening of atopic dermatitis, by stimulating and maintaining Th2-driven inflammatory reactions. In collaboration with the epidemiology WG, it is investigated whether a gain-of-function polymorphism in the coding region of the AKR1C3 gene is associated with an enhanced individual susceptibility to airborne particulate matter-associated atopic dermatitis.

Between 2020 and 2022, this WG published 5 papers on average per year, exclusively in peer-reviewed journals; an average 4 of which were co-authored with other WGs. Its third-party revenues totalled 133k € on average per year. Third-party funding comes from the DFG (⌀ 104k €) and the Jürgen Manchot Stiftung (⌀ 30k €). One PhD degree and one habilitation were completed.

WG Krutmann: Environmentally induced skin ageing

5.2 FTE, of which 3.4 FTE Research and scientific services and 1.8 FTE Service staff]

This WG investigates the molecular mechanisms that underlie environmentally-induced skin ageing and associated skin diseases. Major discoveries include: (1) the observation that the AHR is critically involved in the UVB stress response; (2) a potentially curative therapeutic approach for the UV-sensitive progeroid Cockayne syndrome; (3) the identification of traffic-related air pollution as a causative factor for skin ageing/pigmentation; (4) the identification of near infrared rays as causative for skin wrinkle formation; (5) the definition and characterization of the skin ageing exposome; (6) the development of an ectoine-based medical product for the protection against particle-induced lung diseases; (7) the identification of two cutotypes in the skin microbiome of Han Chinese.

Between 2020 and 2022, this WG published 16 papers on average per year, mainly in peer-reviewed journals; an average 5 of which were co-authored with other WGs. Its third-party revenues totalled 689k € on average per year. Third-party funding mostly comes

from the Leibniz Association (⌀ 277k €), federal and *Länder* governments (⌀ 191k €), and the DFG (⌀ 134k €). The WG filed a total of 2 patents. One PhD degree was completed.

WG von Mikecz: Environmental noxae and cell nucleus

3.8 FTE, of which 2.7 FTE Research and scientific services, 0.7 FTE Doctoral candidates, and 0.5 FTE Service staff]

Identifying nanomaterial-bio-interactions is imperative due to the broad introduction and distribution of nanoparticle applications. This WG investigates gene expression in the genetically amenable animal model *C. elegans*, which has a simple nervous system with differentiated neural wiring and neurochemistry. In *C. elegans*, nanoparticle effects range from induction of amyloid in nucleoli of intestinal cells and disturbance of intestinal function to facilitation of protein aggregation in body wall muscles and axons of neural cells. Proteomic screening identifies segregation of proteins belonging to the gene ontology group of protein homeostasis in an SDS-resistant aggregome network. Network proteins include chaperones, heat shock proteins and the 26S proteasome, all involved in protein homeostasis. Comparative proteomics show that pollutants corrupt the resilience pathways of ageing. The analysis of reporter worms for serotonergic and dopaminergic neural cells reveals xenobiotic-induced protein aggregation in axons of single *C. elegans* neurons, where presynaptic accumulation of neurotransmitters, e.g. disturbed axonal transport reduces the capacity for neural function. This in turn causes neurodegeneration and accelerates the decline of age-related behaviors indicating a reduced health span by certain nanomaterials.

The WG applies life span-resolved nanotoxicology in the animal model *C. elegans*, e.g. observation of pollutant effects in young, middle-aged and old worms. This strategy aims at identifying vulnerable age-groups and molecular pathways of susceptibility that offer opportunities for beneficial interventions. To characterise the role of air pollution in neurodegenerative protein aggregation diseases such as Alzheimer's and Parkinson's, *C. elegans* models for neurodegenerative diseases are used to investigate molecular effects of traffic-related nanomaterials. Collaboration within the IUF and consequent application of transcriptomics and proteomics targets at translating the findings from *C. elegans* to higher order organisms, including human cohorts, and validate the concept of one health.

Between 2020 and 2022, this WG published 2.3 papers on average per year, mainly in peer-reviewed journals; an average 0.3 of which were co-authored with other WGs. Its third-party revenues totalled 119k € on average per year, almost exclusively from the DFG. One PhD degree was completed.

WG Schikowski: Environmental epidemiology of lung, brain and skin ageing

[8.8 FTE, of which 2.0 FTE Research and scientific services, 1.3 FTE Doctoral candidates, and 5.5 FTE Service staff]

The WG focuses on the epidemiology of environmentally-induced effects on the lungs, brain, and skin. The WG maintains the long-term SALIA and GINIplus cohorts with the main focus on the regular collection of health data and analysis of data on the effects of

environmental exposures (air pollution, temperature, and greenspace) on chronic diseases and the complex interactions between the organs. The group was among the first to show that traffic-related air pollution is associated with chronic obstructive pulmonary disease (COPD), skin ageing, and the risk of developing mild cognitive impairment. Also, the group is part of the NAKO study (German National Cohort) and maintains the study centre in Düsseldorf together with the German Diabetes Centre (DDZ), a fellow Leibniz institute. The group is involved in several large cohorts in China, India, and Japan.

Between 2020 and 2022, the WG published 18 papers on average per year, mainly in peer-reviewed journals; an average 3 of which were co-authored with other WGs. Its third-party revenues totalled 266k € on average per year; 149k € of which were received for the NAKO study and 71k € from the DFG. Four medical doctorates were completed.

WG Schins: Particles, inflammation and genome integrity

[4.7 FTE, of which 3.0 FTE Research and scientific services, 0.7 FTE Doctoral candidates, and 1.0 FTE Service staff]

The WG investigates the cellular and molecular mechanisms of toxicity of inhaled and ingested particles. The group's research contributed to understanding the importance of inflammation in the pathogenesis of particle-induced diseases. This indirect mode of action has become an integral part of the scientific and regulatory assessment of inhalable dusts and engineered nanomaterials. Current projects address effects of mineral dusts, transport-derived ultrafine particles, and engineered (nano)materials on genome integrity, and tissue remodeling processes in the respiratory tract, the gastrointestinal tract, and the central nervous system. The research in these projects focuses on the identification of underlying intercellular and interorgan crosstalk mechanisms. The group is also committed to the development of new approach methods for the hazard assessment of particles, through advancement and validation of realistic *in vitro* models of the lung and the intestine.

Between 2020 and 2022, the WG published 9 papers on average per year, mainly in peer-reviewed journals; an average 2 of which were co-authored with other WGs. Its third-party revenues totalled 188k € on average per year. Third-party funding mostly comes from the EU (⌀ 107k €). Two doctoral degrees were completed.

Core units

Core unit Rossi: Genome engineering and model development (GEMD)

The GEMD unit, founded in 2019, provides scientific support for laboratories inside and outside the IUF. The core expertise of the GEMD comprises the generation of genetically modified cells, reprogramming of somatic cells into induced pluripotent stem cells (iPSCs), generation of iPSCs-derived organoids, sequencing, and bioinformatic analysis. The lab has also established its own research program by developing new tools in the field of genome engineering and sequencing, and by studying the relationship between genetic compensation and pollution.

Core unit Schikowski: Computational exposure assessment (CEA)

The purpose of the CEA unit, which was established in 2020, is to contribute to the assessment of health effects caused by environmental exposures by developing state-of-the-art bioinformatic and statistic methods for the modelling of publically available or specifically generated large data sets of environmental exposures. In this context, it develops e.g. small-scale methods for exposure estimation in urban areas like the Ruhr area or Delhi.

Scientific infrastructure

Animal facility

The animal facility provides the opportunity to keep and breed wildtype and transgenic rodent animals that are used as *in vivo*-models in all four research fields. Besides the supply of animals for experiments, the unit offers the opportunity to handle and expose animals under specified pathogen free (SPF) conditions. To accomplish this goal, the facility is designed as a user-open unit in which researchers can perform experiments and analyses on site supported by members of the staff. Therefore, the facility is frequently used for multiple research approaches including irradiation studies, microbiome analysis, and inhalation studies. Specifically for the investigation of the health effects of traffic-dominated air pollutants, the IUF has created an infrastructure on its premises for controlled inhalation exposure studies of rodents.

During the last two years, the structural conditions of the building were significantly upgraded in order to match state-of-the-art technical and hygienic standards. These extensive modifications allow running three SPF units equipped with newly supplied autoclaves and two units for experimental applications. The standardised keeping conditions are achieved by the use of individually ventilated cage systems combined with decentral humidity-controlled ventilation devices. Thus, air quality is particularly low in pathogen and particle burden. Due to these technical preconditions and a close pathogen monitoring, the animal facility is able to provide animals with a hygiene standard that is indispensable for studies with environmental pollutants.

Transgenic or knock-out animals can be kept and bred as the whole facility is registered under biosafety level 1 (S1 GenTSV). The animal facility puts particular emphasis on the implementation of the 3R concept. The high quality and hygienic standards combined with the consideration of the specific needs of animals for their well-being contributes to the refinement of animal experiments. A breeding management, which is closely monitored together with the facility users, aims to reduce animal numbers.

Human *in vivo* studies

In this unit, human volunteers and patients from clinical centres are recruited in order to assess and verify results from *in vitro* systems and from animal models in humans *in vivo* as proof of concept trials and as randomised placebo-controlled intervention studies to assess the efficacy of novel preventive strategies. These include e.g. extremolyte containing inhalation solutions, topical actives, and nutritional supplements, which were tested

for their efficacy to protect from lung inflammation, acute bronchitis, and acute respiratory infections, and ultraviolet radiation and air pollution-induced skin ageing as well as from environmentally-induced imbalance of the skin microbiome.

The access to human tissue from volunteers for comparison of exposed versus unexposed sites or for isolation of primary cells and their culture in the biosafety level 2 laboratories allow observational and mechanistical studies and further expansion of a human dermal fibroblast biobank. Blood samples from volunteers are also taken to isolate human peripheral blood mononuclear cells.

FACS

The FACS unit offers the use of its two flow cytometers to all research fields that need flow cytometric analysis and/or sorting. Sorted cells can be further cultivated or processed for molecular biological investigations. A MACS® magnetic cell sorter for pre-enrichment of rare cells is available as well.

Imaging

The fluorescence microscopy facilities are located on two sites. They include facilities that allow imaging of optical sections and that provide the possibility of microinjection. Investigations which are conducted with fluorescence microscopes are, e.g., the localisation of proteins or changes in protein expression during cell differentiation, the differentiation of neurospheres, and the development of *C. elegans*. The GEMD unit additionally provides a microscope that enables fluorescent live cell imaging and imaging of fixed specimen on object slides. Two inverse fluorescence microscope systems for high content imaging are available. Both allow scanning of complete multiwell plates, e.g. for automatic quantification of cell types or for analysis of cell morphology in 2D cell cultures. The systems are mainly used for the analysis of complex 3D cell cultures like the neurosphere model. To this end, an advanced software was developed at the IUF which allows the quantification of cell types and neurosphere specific endpoints like migration distance and cell distribution as well as neuronal differentiation and neuron morphology. In addition, a deep learning approach for identification and quantification of cell types (neurons and oligodendrocytes) in microscopic images from differentiated primary human neurospheres was established and validated. This approach performs with high accuracy and is robust against typical potential confounders, and hence can be used for studying compound effects on neural differentiation processes in an automated and unbiased process.

S2 laboratories

The IUF operates two central biosafety level 2 laboratories. They are mandatory for highly efficient transductions of primary cells employing lentiviral particles. Moreover, biosafety level 2 laboratories allow isolation of cells and cultivation of human material from human donors not negatively tested for HIV, HBV, and HVC. These laboratories also provide imaging and FACS facilities. Users of these central units get technical support/training by the imaging/FACS experts, and administrative/technical support by the project leaders for the mandatory registration of the planned additional biosafety level 2 projects with the local authorities in advance.

8. Handling of recommendations from the previous evaluation

The IUF responded as follows to the recommendations of the last external evaluation (highlighted in italics, see also statement of the Senate of the Leibniz Association issued on 23 November 2016, pages B-3 ff.):

1) *"Establishing a 'Model Development' core unit is a key strategic measure for the IUF's development. The methodological expertise combined within this unit plays a significant role in implementing the IUF's long-term scientific objectives. It is explicitly recommended that this measure be implemented with additional resources, based on an extraordinary item of expenditure [i.e. an increase in institutional funding]."*

The core unit GEMD has been established since 2018 (see chapter 7).

2) *"In 2007, the German Science and Humanities Council (Wissenschaftsrat) considered the planned new institute building to be urgently necessary. For the time being, however, the IUF is housed in a Land-owned facility. In past years, some of the building's defects were remedied using additional resources provided by the funders. These resources were invested in the lab area, in the lab-animal facilities, and in fire protection measures, among others. The existing rental agreement was terminated by Bau- und Liegenschaftsbetrieb Nordrhein-Westfalen (BLB) as of the end of 2017 due to the deteriorating building structure and the resulting operational inefficiency. So far it is still unclear where the IUF will be housed starting in January 2018. It is urgently necessary to resolve the issue of permanent accommodation, which must be addressed quickly by the responsible parties. In addition, moving the Institute twice within a short period of time is absolutely to be avoided. Negotiations regarding the IUF's remaining in the current facilities until permanent accommodation is secured must be concluded in a positive way by the responsible parties very soon."*

   In July 2016, the Leibniz Senate stated as a result of this assessment by the review panel: *"Currently, the IUF is housed in a Land-owned property whose building fabric is dilapidated. The lease with the Bau- und Liegenschaftsbetrieb Nordrhein-Westfalen ends in 2017 and it is still unclear how the IUF will be housed from January 2018. The Senate calls on those responsible to clarify the question of appropriate permanent accommodation for the IUF without delay, and asks the supervisory board of the IUF to report on this by 31 March 2017."*

   In July 2017, the Senate stated the following with regard to the resulting report: *"The Senate welcomes the present plans for a new building for the institute, which must now be implemented quickly. Furthermore, it welcomes the decision of those responsible that the IUF can remain in the property currently used by the Institute until the new building is completed."*

The limited rental agreement was made permanent. A new building is planned and expected to be constructed by 2027.

3) *"At the time of the evaluation, the IUF still had a binding staffing plan in place. The responsible Land department is expected to suspend the binding nature of the staffing plan for*

employees covered by collective wage agreements, according to the decision on implementing the Execution Agreement for the Leibniz Association (AV-WGL), and to replace it with criteria that allow for global workforce management."

The regulation was changed accordingly in 2017.

4) *"The partnership with the LIMES institute at the University of Bonn is very productive for the IUF and should be further systematised."*

The LIMES leader's Leibniz Chair at the IUF was renewed in 2020, and further joint DFG-funded projects of the IUF and the Liaison group at LIMES/University of Bonn were carried out. A junior research group, possibly including a jointly appointed junior professor, will possibly be established in 2023.

5) *"The review board is pleased that the IUF, using its own resources, established junior research groups in 2008, 2011, and 2013, as recommended by the German Science and Humanities Council (Wissenschaftsrat). It is good that the Scientific Advisory Board evaluates these groups at three-year intervals. However, it still remains unclear how long the IUF will support these junior research groups at the most. It is also unclear whether the institute plans to offer an option for these groups to become permanent. This question must urgently be clarified. The IUF offers an outstanding working environment for junior research groups. As suggested by the Scientific Advisory Board, it is recommended that opportunities for third-party funding (e.g. the Emmy Noether Program) also be used in order to establish junior groups at the institute."*

Both junior research groups were promoted to regular working groups in 2016. Two new junior research groups are expected to take up work in 2023.

6) *"In past years, the institute faced the challenge of repeatedly spending significant funds on repair work to the building structure, which the landlord described as dilapidated, that could not be delayed. It is understandable that the performance-based funding allocation (PFA) system established at the IUF had to be suspended by the management during this time, that resource commitments for working groups could not be realised within the planned scope or time frame, and that it was also not possible to finance additional Abel fellowships or so-called 'bridge projects' to support work across research fields. As already recommended by the Scientific Advisory Board, however, the PFA should be reactivated as soon as the institute's financial situation allows. The management must agree with the group leaders on appropriate, reliable resource plans that take the known challenges into account, and must communicate its decisions about the allocation of funds to all IUF employees in a clear, transparent manner."*

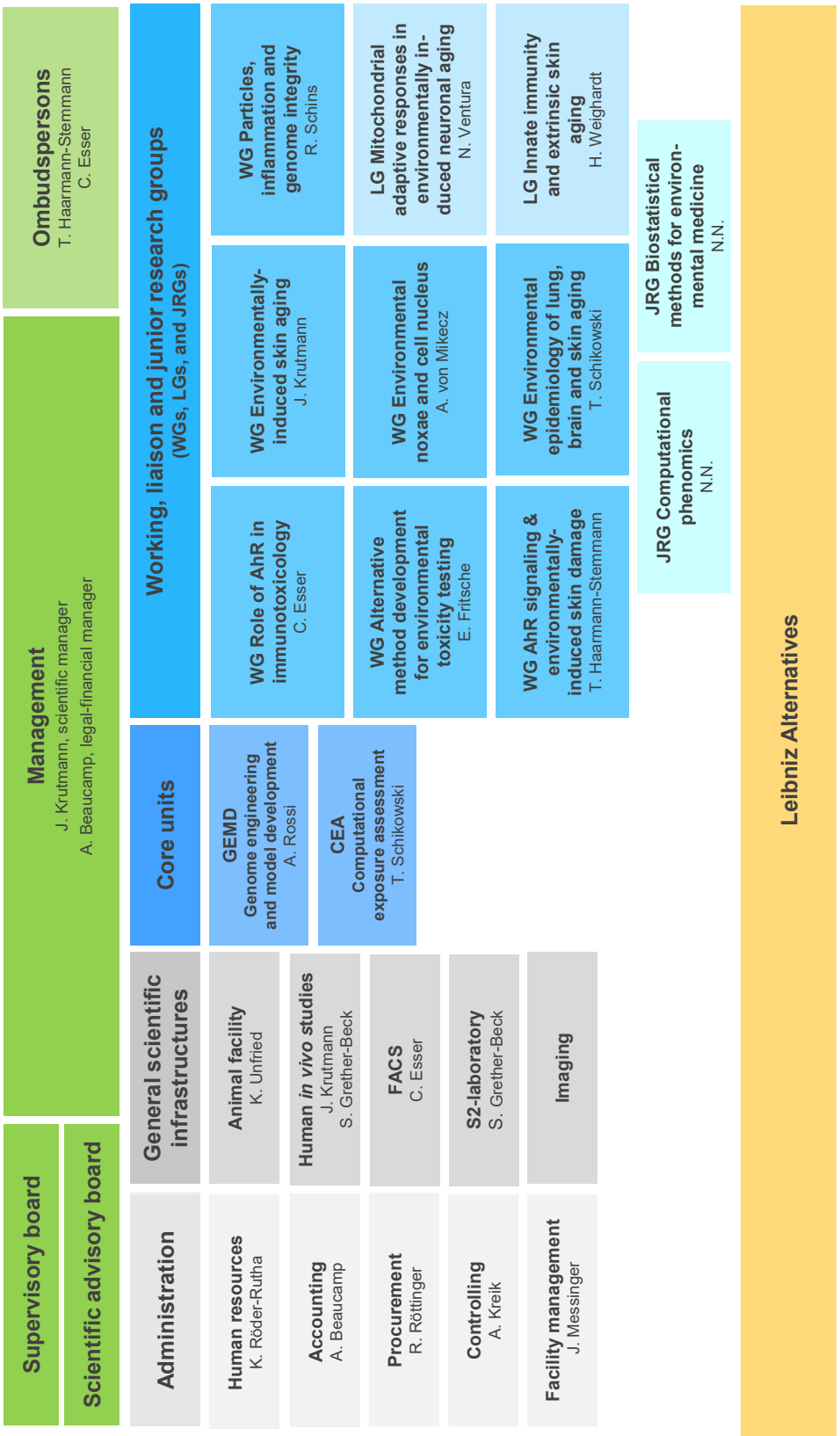
By the end of 2017, the financial situation has stabilised. The PFA was gradually put in place again and fully reactivated in 2019. According to the IUF, the financial situation is communicated and discussed in a transparent and open manner.

7) *"As requested by the Senate, the Scientific Advisory Board should perform an audit of the entire institute between two external evaluations in the future. The annual minutes of the Scientific Advisory Board meetings do not replace the audit requested by the Senate."*

An audit was scheduled for spring 2020. Due to the pandemic, it was first rescheduled and then conducted remotely in April 2021.

Appendix 1

Organisational Chart



Appendix 2
Publications, patents, and expert reviews

	Period		
	2020	**2021**	**2022**
Total number of publications	**68**	**80**	**82**
Individual contributions to edited volumes	2	4	0
Articles in peer-reviewed journals	64 (+ 14*)	75	82 (+4)
Articles in other journals	1	0	0
Working and discussion papers	0	1	0
Editorship of edited volumes	1	0	0

*14 co-authorship papers from the NAKO cohort in 2 special issues

Patents	**2020**	**2021**	**2022**
Applications giving rise to a right of priority (in the calendar year)	1	0	2

Other industrial property rights[1)]	**2020**	**2021**	**2022**
Property rights (number held as of 31.12. of the year)	1	1	2

[1] Concerning financial expenditures for revenues from patents, other industrial property rights and licences see Appendix 3.

Appendix 3

Revenue and Expenditure

Revenue		2020			2021			2022[1]		
		k€	%	%	k€	%	% [3]	k€	%	%
Total revenue (sum of I., II. and III.; excluding DFG fees)		10,861			11,946			11,620		
I.	**Revenue (sum of I.1., I.2. and I.3)**	**10,861**	**100%**		**11,946**	**100%**		**11,620**	**100%**	
1.	INSTITUTIONAL FUNDING (EXCLUDING CONSTRUCTION PROJECTS AND ACQUISITION OF PROPERTY)	8,449	78%		8,805	74%		8,420	73%	
1.1	Institutional funding (excluding construction projects and acquisition of property) by Federal and *Länder* governments according to AV-WGL	8,449			8,805			8,420		
1.2	Institutional funding (excluding construction projects and acquisition of property) not received in accordance with AV-WGL	0			0			0		
2.	REVENUE FROM PROJECT GRANTS	**2,412**	**22%**	**100%**	**3,144**	**26%**	**100%**	**3,200**	**27%**	**100%**
2.1	DFG	784		32%	747		24%	634		20%
2.2	Leibniz Association (competitive procedure)	168		7%	340		11%	411		13%
2.3	Federal, *Länder* governments [2]	830		34%	780		25%	53		2%
2.4	NAKO study	130		5%	197		6%	120		4%
2.5	EU	264		11%	596		19%	749		23%
2.6	Industry	119		5%	206		7%	454		14%
2.7	Foundations	87		4%	83		3%	262		8%
2.8	International public sector [3]	0		0%	119		4%	518		16%
2.9	Other sponsors	31		1%	76		2%	0		0%
3.	REVENUE FROM SERVICES	0	0%		0	0%		0	0%	
II.	**Miscellaneous revenue** (e.g. membership fees, donations, rental income, funds drawn from reserves)	0			0			0		
III.	**Revenue for construction projects** (institutional funding by Federal and *Länder* governments, EU structural funds, etc,)	0			0			0		

Expenditures		k€	k€	k€
Expenditures (excluding DFG fees)		**10,665**	**11,731**	**11,620**
1.	Personnel	7,224	7,981	8,002
2.	Material expenses	1,057	1,382	1,420
3.	Equipment investments	920	952	750
4.	Construction projects, acquisition of property	0	0	0
5.	Other operating expenses	1,464	1,416	1,448

DFG fees (if paid for the institution – 2,5% of revenue from institutional funding)	198	199	202

[1] Preliminary data: yes

[2] Revenue from projects grants, 2.3 Federal, Länder governments: strong decrease of revenues in 2022 because of scheduled projects end in 2021. For example: KAUVIR TP A, KAUVIR TP C, CERST NRW, VIP+.

[3] New third-party donor in 2021: The Danish Environmental Protection Agency (DK-EPA); in 2022: National Institutes of Health (USA)

Appendix 4

Staff

(Basic financing and third-party funding / proportion of women (as of: 31/10/2022)

	Full time equivalents		Persons		Women		for-eigners
	Total	on third-party funding	Total	on temporary contracts	Total	on temporary contracts	Total
	Number	Percent	Number	Percent	Number	Percent	Number
Research and scientific services	**46.1**	**35 %**	**52**	**59 %**	**32**	**22 %**	**10**
1st level (scientific directors)	1	-	1	-	-	-	-
2nd level (department leaders or equi.)	-	-	-	-	-	-	-
3rd level (group leaders or equi.)	6	-	6	-	4	-	1
Junior research group leaders (if applicable)	-	-	-	-	-	-	-
Further academic staff in executive positions	3	-	3	-	-	-	1
Scientists in non-executive positions (A13, A14, E13, E14 or equivalent)	28.3	41 %	30	63 %	21	14 %	7
Doctoral candidates (A13, E13, E13/2 or equi.)	7.8	58 %	12	100 %	7	57 %	1
Science supporting staff (laboratories, technical support etc.)	**30.7**	**9 %**	**34**				
Laboratory (E9 to E12,upper-mid-level service)	14.2	18 %	17				
Laboratory (E5 to E8, mid-level service)	3.6	3 %	4				
Animal care (E5 to E8, mid-level service)	7	-	7				
Technical (large equipment, service) (E5 to E8, mid-level service)	5.9	-	6				
Science supporting staff (administration)	**12.3**	**-**	**13**				
Head of the administration	1	-	1				
Staff positions (from E13, senior service)	2	-	2				
Staff positions (E9 to E12, upper-mid-level service)	2	-	2				
Internal administration (financial administration, personnel etc.) (E8 to E12, upper-mid-level service)	6.3	-	7				
Building service/Warehouse staff (E1 to E4)	1	-	1				
Student assistants	**2.7**	**81 %**	**9**				
Trainees	**1**	**-**	**1**				
Scholarship recipients at the institution	**2**	**100 %**	**3**		2		-
Doctoral candidates	2	100 %	3		2		-

11 June 2023

Annex B: Evaluation Report

Leibniz Research Institute for Environmental Medicine, Düsseldorf (IUF)

Contents

1. Summary and main recommendations

The Leibniz Research Institute for Environmental Medicine (IUF) conducts research on the impacts of environmental stressors on the human body. It focuses on three organs: the lungs, skin and central nervous system. The core methodological areas of expertise at the IUF are toxicology, immunology and epidemiology, including bioinformatics.

The research carried out at the IUF is relevant, innovative and of a high standard. The institute has implemented sensible consolidation measures and has more sharply delineated its scope of work, in particular by now having a greater focus on barrier organs. Recently, capitalising on many years of accumulated expertise in various environmental medical fields, the institute has increasingly been investigating inter-organ crosstalk and asking to what extent human phenotype and age groups differ in terms of their susceptibility to certain environmental stressors. The IUF successfully exploits the high potential for research transfer, primarily through the provision of advisory services for regulatory authorities. It has been particularly successful in developing alternatives to animal experiments. The IUF is now facing a time of change, since the scientific manager, who has led and shaped the institute successfully for over 20 years, will be retiring by 2026 at the latest, as will other senior staff members in the coming years.

Three of its working groups and core units are rated 'excellent', two 'very good to excellent' and three 'very good'. The establishment of the two core units on 'Genome Editing and Model Development' and 'Computational Exposure Assessment', for which the federal and *Länder* governments increased the IUF's institutional funding in 2018 and 2020, is particularly promising for future lines of research. It is very good to see that the working groups now have a basic level of resources that they can rely on and that performance-based funding allocation (PFA) to the groups was reintroduced in 2019, as was recommended seven years ago.

The IUF has €11.5 million per year available for ongoing activities (⌀ 2020–2022), of which a quarter currently comes from third parties. In a positive development, a DFG Research Unit led by the IUF started work in January 2023.

The IUF has established suitable measures to safeguard good scientific practice. The publication strategy is convincing, and a pleasingly high proportion (most recently 87%) of studies are published via open access routes. In the area of animal husbandry and animal experiments, the IUF consistently follows the recognised principle of the 3Rs.

Scientific staff at the IUF have very good training options. A structured doctoral program has been in place since 2011 and works very well. The proportion of women in research is pleasingly high, and the IUF has taken suitable measures to allow staff to combine career and family.

The IUF has very good working relationships with scientific partners. Joint appointments are in place or in progress with three universities. The research benefits considerably from the institute's close collaboration with partners, particularly in the Netherlands and Asia.

Special consideration should be given to the following main recommendations in the evaluation report (highlighted in **bold face** in the text):

Overall concept, activities and results (chapter 2)

1. The focus on three organs (lungs, skin and central nervous system) and three core areas of expertise (toxicology, immunology and epidemiology/bioinformatics) is good and also makes sense in light of the institute's limited resources. In practice, and for good reason, the research activities concentrate on individual environmental stressors. Instead of implementing an even further-reaching approach as outlined in the documentation, the IUF is recommended to maintain this convincing **basic concept** and further hone its profile based on it.
2. To link the individual groups, the IUF has established four **research fields**, three of which deal with the research organs and one with the immune system. The focus on organs makes sense, but the task of the methodologically oriented 'immune system' research field is still vague. The IUF needs to strategically clarify its function and the interrelationship between the research organs and the methodological expertise. Subsequently it can define the research fields in terms of both content and the way they work. A suitable forum should be set up for these kinds of strategic deliberations, for instance in the form of regular retreats.

Changes and planning (chapter 3)

3. The convincing focus of the overall concept on three organs and three core methodological areas of expertise calls for structural, systematically coherent decisions – particularly for the fundamental question of which local universities the IUF will work with in future, how the important connection to university medicine can be secured in the long term, and for which areas of expertise joint appointments are to be arranged. **Strategic considerations** concerning these matters, which transcend case-by-case decisions, are not yet sufficiently apparent. It is the role of the Supervisory Board to clarify this in good time, especially in view of the upcoming appointment procedures.
4. A new leader of the institute needs to be appointed by 2026 at the latest. It makes sense to appoint a successor who has expertise in one of the three research organs too. Also, the head of one of the working groups, who is the repository of most of the immunological expertise at the institute, could retire as early as 2024, unless she carries on working for longer. Given that the toxicology area has a link to a local university through a **joint appointment to a professorship** – as epidemiology/bioinformatics will again in future – the institute should strive to make a similar arrangement for immunology. The two positions must be filled within a strategic context, and the decision about filling the immunology position should only be taken after a new scientific manager has been appointed.

Controlling and quality management (chapter 4)

5. The IUF continues to use outdated premises with dilapidated **building** fabric, including for its animal husbandry activities. Back in 2007, the German Science and Humanities Council considered the new building planned at the time by the *Land* to be urgently necessary. This was backed by the Leibniz Senate in 2016. After a long delay, construction is now due to start in summer 2024, with the handover anticipated for

summer 2027. As requested by the Scientific Advisory Board, the new building must have sufficient spaces and rooms for informal communication.

6. The IUF should introduce an **electronic laboratory notebook** system (ELN).
7. It is expected that members of the **Scientific Advisory Board** stand down after their second term of office, at the latest, as stipulated by the Leibniz Association Senate and as recommended during the last evaluation. A relatively high proportion of Scientific Advisory Board members are no longer in active employment. This should be amended, and there should be a greater balance in terms of age structure.

Human resources (chapter 5)

8. The IUF is advised to promote **staff exchanges** with other institutions much more intensively. In particular, it should secure more external scientists for positions or visiting residencies at the institute. Likewise, more junior researchers from the IUF should be encouraged to take up residencies at other institutions or to move to other institutions following their qualification phase.
9. The number of PhDs completed at the IUF has fallen from approx. 8 per year (2013–2015) to approx. 3 per year (2020–2022). At the same time, the number of doctoral researchers employed at the institute has fallen from 25 (2015) to 15 (2022). The IUF must increase its **PhD numbers** again. The participation of IUF professors in two DFG-funded Research Training Groups since 2021 and the planned further joint appointments to professorships offer very good conditions for this.

Subdivisions of the IUF (chapter 7)

10. The **CEA core unit** was established from 2020 onwards with additional institutional funds from the federal and *Länder* governments (€280,000 p.a.), which were added to the core budget in 2022. The CEA's mission is to develop models for small-scale exposure assessment in metropolitan areas, for example in India. The startup phase of this core unit is not yet completed, partly because of unforeseen staff turnover, which means that it is currently understaffed with fewer than one FTE researcher. It is currently being led by a working group leader alongside her other tasks. In order for the unit to be able to work on its very promising tasks, the startup phase must be completed quickly. In particular, the planned coordinator position needs to be filled soon at an internationally competitive level.

2. Overall concept, activities and results

Overall concept

The Leibniz Research Institute for Environmental Medicine (IUF) conducts research on the impacts of environmental stressors on the human body. It focuses on three main research organs: the lungs, skin and central nervous system. The choice of organs has been clearly and coherently defined. The core methodological areas of expertise at the IUF are toxicology, immunology and epidemiology, including bioinformatics.

The focus on three organs (lungs, skin and central nervous system) and three core areas of expertise (toxicology, immunology and epidemiology/bioinformatics) is good and also makes sense in light of the institute's limited resources. In practice, and for good reason, the research activities concentrate on individual environmental stressors. Instead of implementing an even further-reaching approach as outlined in the documentation, the IUF is recommended to maintain this convincing basic concept and further hone its profile based on it. In view of this, the IUF should divest itself of two approaches that generate far-reaching and hardly achievable expectations regarding the scope of its work: Firstly, it is reasonable that, in practice, organ ageing barely features in the work of the institute. It should not overextend itself with the ambitious goal of working in this field as well. Secondly, the practical implementation of an approach that goes beyond individual stressors to study the exposome as a whole would exceed the institute's means.

The scientific work at the IUF currently takes place in seven working groups that are very successful in their respective fields. Some of them have a strong international profile. They have recourse to support from two new core units, which sometimes conduct research themselves, and from other facilities.

To link the individual groups, the IUF has established four research fields, three of which deal with the research organs and one with the immune system. The focus on organs makes sense, but the task of the methodologically oriented 'immune system' research field is still vague. The IUF needs to strategically clarify its function and the interrelationship between the research organs and the methodological expertise. Subsequently it can define the research fields in terms of both content and the way they work. A suitable forum should be set up for these kinds of strategic deliberations, for instance in the form of regular retreats.

Results

Research

The research conducted at the IUF is relevant, innovative and of a high standard. The institute's many years of continuous research on the aryl hydrocarbon (Ah) receptor have earned it a leading role in this field. The institute also regularly produces impressive results in fields like research into the impact of UV radiation on the skin and neurotoxicology research. Recently, the institute has increasingly been investigating inter-organ crosstalk, based on its expertise in these kinds of areas, and asking to what extent human phenotype and age groups differ in terms of their susceptibility to certain environmental stressors (susceptible groups). The institute's studies are generally published internationally and often earn visibility beyond individual specialist communities.

Infrastructure

The IUF provides valuable epidemiological research infrastructure. It runs the SALIA and GINIplus cohorts, the latter of which jointly with partners. It is also one of four Leibniz institutes involved in the German National Cohort (NAKO) and runs the NAKO study centre in Düsseldorf in collaboration with the German Diabetes Centre – Leibniz Institute for Diabetes Research (DDZ).

Transfer

The IUF's focus on environmental medicine, which is highly relevant to society, holds great potential for successful research transfer. It exploits this potential primarily through the provision of advisory services for regulatory authorities. In the area of technology transfer, the IUF collaborates with partners with a proven track record in the relevant fields, such as patent law. It has had particular success with the development of an *in vitro* test battery for developmental neurotoxicity. It is a very good achievement that a start-up company was recently spun off for this purpose and has been awarded several prizes.

3. Changes and planning

Development since the previous evaluation

In recent years, the IUF has carried out sensible consolidation measures and has more sharply delineated its scope of work. For instance, the research programme now has a greater focus on barrier organs. The concentration of the institute's activities reduced the number of working groups from ten to seven. It is very good to see that, as recommended, the working groups now have a basic level of resources that they can rely on: they now each have central funding for a postdoc and a technician, as well as a group leader. In addition, the performance-based funding allocation system (PFA), which had been suspended at the time of the last evaluation, has now been reinstated.

The institute has also for some time been expanding its activities in epidemiology and bioinformatics. Seven years ago, there were two units working in this field; in future there will be five. The federal and *Länder* governments increased the IUF's institutional funding in 2018 and 2020 for the establishment of two particularly promising core units: Genome Editing and Model Development (GEMD) and Computational Exposure Assessment (CEA). By setting up GEMD and promoting a junior research group to a regular working group, the institute has largely managed to compensate for the loss of a working group on environmental epidemiology. The CEA unit is still in development (see chapter 7). In addition, appointment procedures are currently running for tenure-track junior professorships in biostatistics and computational phenomics. The expansions mentioned must be accompanied by close collaboration between the groups and their leaders.

The Leibniz Alternatives platform was developed for collaboration with public- and private-sector clients. It develops and validates alternatives to animal experiments for neurotoxicity testing and transfers them into application. It will be expedient to draw on the progress made in this area also for the IUF as a whole and the other working groups.

Strategic work planning for the coming years

The convincing focus of the overall concept on three organs and three core methodological areas of expertise calls for structural, systematically coherent decisions – particularly for the fundamental question of which local universities the IUF will work with in future, how the important connection to university medicine can be secured in the long term, and for which areas of expertise joint appointments are to be arranged. Strategic considerations concerning these matters, which transcend

case-by-case decisions, are not yet sufficiently apparent. It is the role of the Supervisory Board to clarify this in good time, especially in view of the upcoming appointment procedures.

Because of its history, the IUF has always had significant links to the University of Düsseldorf, particularly its Faculty of Medicine. Seven years ago, this led to four joint appointments to professorships. As a result of the cardiovascular work coming to an end, and the changes in epidemiology, the number of joint appointments has been reduced to the institute's scientific manager, who is a dermatologist, and one working group leader, who is a toxicologist. The field of epidemiology/bioinformatics is no longer worked on in collaboration with the University of Düsseldorf, but will in future have joint appointments with the universities in Bochum and Dortmund. In addition, the IUF maintains links to the LIMES Institute at the University of Bonn, which have been strengthened in recent years.

A new leader of the institute needs to be appointed by 2026 at the latest. It makes sense to appoint a successor who has expertise in one of the three research organs too. Also, the head of one of the working groups, who is the repository of most of the immunological expertise at the institute, could retire as early as 2024, unless she carries on working for longer. Given that the toxicology area has a link to a local university through a joint appointment to a professorship – as epidemiology/bioinformatics will again in future – the institute should strive to make a similar arrangement for immunology. The two positions must be filled within a strategic context, and the decision about filling the immunology position should only be taken after a new scientific manager has been appointed.

4. Controlling and quality management

Facilities, equipment and funding

The IUF receives sufficient institutional funding. The total annual budget is €11.5 million (⌀ 2020–2022), of which currently a quarter (⌀ €2.9 million per year) comes from third parties. This is a good level of third-party funding, although it is slightly lower than at the last evaluation (⌀ 2013–2015: 29%). In a very good achievement, the IUF recently secured competitive third-party funding through its involvement in the DFG Research Unit 5489, which it coordinates.

The IUF continues to use outdated premises with dilapidated building fabric, including for its animal husbandry activities. Back in 2007, the German Science and Humanities Council considered the new building planned at the time by the Land to be urgently necessary. This was backed by the Leibniz Senate in 2016. After a long delay, construction is now due to start in summer 2024, with the handover anticipated for summer 2027. As requested by the Scientific Advisory Board, the new building must have sufficient spaces and rooms for informal communication.

Organisational and operational structure

The current scientific manager, who has held office since the institute was founded in 2001, has successfully developed the IUF. It is largely thanks to him that it was admitted to the joint

federal and *Länder* funding programme in 2011. His working relationship with the legal and financial manager, who has also been in position for many years and is responsible for the administrative area, is characterised by mutual trust and efficiency. The commendable increase in the number of jointly appointed professorships will make it possible in future to relieve the scientific manager of micromanagement tasks.

Quality management

The IUF has established suitable measures to safeguard good scientific practice and has appointed ombudspersons from among the working group leaders. Doctoral researchers have a one-to-one meeting with the scientific manager at the start of their project, during which, among other things, the rules in place at the institute are explained. The rule that the original data on which a publication is based must be submitted to the scientific manager in order to be eligible to participate in the performance-based funding allocation system (PFA, see below) is as simple as it is effective. **The IUF should introduce an electronic laboratory notebook system (ELN).**

The publication strategy is convincing and a pleasingly high proportion (most recently 87%) of studies are published via open access routes. The IUF has recently started using preprint servers. This should be pushed further. The researchers are urged to publish also the research data they generate as often as possible. For data protection reasons, however, particularly in the case of cohort studies, this is not always possible. In such cases, the IUF makes the data available individually to members of the scientific community.

In the area of animal husbandry and animal experiments, the IUF consistently follows the recognised principle of the 3Rs. Animals are kept and deployed in line with the legal requirements and the scientific and animal care standards. It is to be expected that the standards in the new building will be higher. The institute is actively and very successfully involved in developing alternative methods, particularly in its toxicology activities.

It is very good to see that performance-based funding allocation (PFA) was reintroduced in 2019, in line with recommendations. On average, the working groups receive about half of the material costs budget provided directly by the IUF through this mechanism. It is a very appropriate incentive system. The IUF should continue to develop the performance indicators defined by the working group leaders, as planned. They are currently based on journal impact factors and secured third-party funding and recognise cross-group collaboration.

Quality management by advisory boards and supervisory board

The Scientific Advisory Board is very involved in supporting the IUF. It is good that it now carries out an audit of the entire institute between two external evaluations, as recommended. **It is expected that members of the Scientific Advisory Board stand down after their second term of office, at the latest, as stipulated by the Leibniz Association Senate and as recommended during the last evaluation. A relatively high proportion of Scientific Advisory Board members are no longer in active employment. This should be amended, and there should be a greater balance in terms of age structure.**

Particularly in view of upcoming tasks of long-term significance, like the new building and the appointment of a new scientific manager, it is important that the Supervisory Board provides the institute with strong commitment and support (see chapter 3).

5. Human resources

Leading scientific and administrative positions

The scientific manager and another working group leader are appointed jointly with the University of Düsseldorf. Appointment procedures are currently underway for two tenure-track professorships in conjunction with the universities in Bochum and Dortmund. The IUF runs recruitment symposia to fill non-professorship leadership positions, and these also produce very good results.

At the beginning of 2028, not very long after the scientific manager retires (see chapter 3), the long-standing legal and financial manager will also retire. It is very good that he, with his many years of experience, will be able to take responsibility for completion of the new building. The Supervisory Board needs to ensure a seamless handover to his replacement.

Staff with a doctoral degree

Postdocs have very good qualification and training opportunities at the IUF. The institute provides access to soft-skills courses and the opportunity to train as a toxicology specialist (European registered toxicologist). In addition, every postdoc is entitled to use €1,000 per year from central institute funds for further training purposes. Since the last evaluation, this has, among other things, led to one working group leader qualifying as a professor (habilitation), and another being appointed to a professorship at a foreign university. The institute's measures should now be developed into a more structured mentoring approach.

The IUF is advised to promote staff exchanges with other institutions much more intensively. In particular, it should secure more external scientists for positions or visiting residencies at the institute. Likewise, more junior researchers from the IUF should be encouraged to take up residencies at other institutions or to move to other institutions following their qualification phase.

Doctoral candidates

The structured doctoral programme, which has been in place since 2011, works very well. The close collaboration with Düsseldorf University's interdisciplinary graduate and research academy, iGRAD, is a great asset. The average length of time to complete a doctorate is reasonable, at 3.7 years.

The number of PhDs completed at the IUF has fallen from approx. 8 per year (2013–2015) to approx. 3 per year (2020–2022). At the same time, the number of doctoral researchers employed at the institute has fallen from 25 (2015) to 15 (2022). The IUF must increase its PhD numbers again. The participation of IUF professors in two DFG-funded Research Training Groups since 2021 and the planned further joint appointments to professorships offer very good conditions for this.

It is good to see that the IUF is now also supervising medical doctorates, in line with recommendations.

Science supporting staff

The IUF is very committed to vocational training. This can be seen, among other things, in the fact that all apprentices are taken on for at least a year following completion of their training. It is good to see that the institute recently started offering an apprenticeship in office administration, alongside the one in animal husbandry. The continuing education and training opportunities are very good. Worth highlighting is the offer to obtain the FELASA B qualification, which is a further qualification for handling laboratory animals.

Equal opportunities and work-life balance

The proportion of women among the scientific staff is still pleasingly high, at 62% overall, and there is a gender balance at the level of working group and core unit leaders.

The IUF has taken suitable measures to allow staff to combine career and family, which led, among other things, to its recertification in the Berufundfamilie Audit.

6. Cooperation and environment

The IUF maintains relationships with a number of university partners, and it is essential that it develops these strategically (see chapter 3). There are currently two joint appointments with the University of Düsseldorf. The IUF plays a significant role in the master's course in toxicology in Düsseldorf. The links to the universities in Bochum and Dortmund have been strengthened structurally through the establishment of jointly appointed junior professorships. There are also close contacts to the LIMES Institute of the University of Bonn, via a liaison group. The head of the LIMES Institute holds a Leibniz Chair at the IUF. The IUF collaborates successfully with its partners in Düsseldorf, Bonn and Dortmund through two DFG-funded Research Training Groups and, recently, in a Research Unit.

The IUF is very well connected within the Leibniz Association. This can be seen especially in its involvement in Research Alliances, research networks, and a Collaborative Excellence project. It has working relationships with the DDZ in Düsseldorf (largely concerning the National Cohort (NAKO) health study), which could be intensified, and also with the FLI in Jena. At national level, the institute's collaboration with Helmholtz Munich deserves a mention, particularly in the field of cohort studies.

The IUF has close scientific contacts to partners in Europe and worldwide. It collaborates productively with the Dutch National Institute for Public Health and the Environment (RIVM) in the field of particle toxicology. Its epidemiology research in particular, but also its phenomics and skin research, benefits greatly from the IUF's collaboration with partners in India (IIT), South Africa (University of KwaZulu Natal), Japan (Kanazawa University) and, despite increasing political challenges, China (Fudan University).

7. Subdivisions of the IUF

WG Esser: "Role of AHR in immunotoxicology"

[4.7 FTE, of which 3.0 FTE research and scientific services staff, 0.7 FTE doctoral candidates, and 1.0 FTE science support staff]

WG Esser has many years of extraordinary expertise in immunotoxicological research on the Ah receptor (AHR), focusing on the skin and intestinal tract as its primary research organs. This group owes its considerable success to the fact that it has worked on its important field of research for decades, largely unaffected by short-term trends.

The working group succeeds in publishing its outstanding research, for example on the importance of the Ah receptor for Langerhans and gamma delta T cells, in very good publications. As a result, it is very highly regarded, also at international level. It plays a central role in the IUF-led DFG Research Unit FOR 5489. The working group is rated as 'very good to excellent'.

WG Fritsche: "Alternative method development for environmental toxicity testing"

[15.1 FTE, of which 6.8 FTE research and scientific services staff, 3.9 FTE doctoral candidates, and 4.4 FTE science support staff]

This working group, which is the largest at the IUF, develops and validates alternatives to animal experiments, particularly in the field of developmental and adult neurotoxicity. With its outstanding research and development activities, which are based on many years of experience, this group is, at an international level, one of the leading research units in its field. One of its particular strengths lies in building and using international networks for validation research.

A particular achievement of this group is the development of an *in vitro* test battery for developmental neurotoxicity, which was supported by EFSA and the OECD. The award-winning start-up DNTOX was recently spun off on the basis of this research. The group's publication record is as impressive as its track record in securing third-party funding, which has tripled since the last evaluation. Moreover, the group keeps on finding new funding bodies, with recent additions being US and Danish authorities. The working group is rated as 'excellent'.

WG Haarmann-Stemmann: AHR signalling & environmentally induced skin damage

[5.1 FTE, of which 2.0 FTE research and scientific services staff, 1.3 FTE doctoral candidates, and 1.8 FTE science support staff]

This group investigates the functions of the Ah receptor in skin cells exposed to environmental stressors. The main aim is to discover new functions through research on agonists and antagonists of the Ah receptor. The work here is therefore a good fit for the IUF's overall research portfolio, and there are numerous interfaces to other working groups.

The working group has developed very well since being promoted from a junior research group in 2016. Its research on individual cells leads to impressive scientific advances, such as the finding that the Ah receptor plays a role in the emergence of radiation-induced skin

cancer. The working group has the potential to build further on its successes in the coming years and to further improve its publication output, which is already good. To this end, the working group should systematically expand its collaboration with other IUF working groups (especially those which do not focus on the skin as their primary research organ) and, by capitalizing on the very good existing models, transfer the promising research approach to broader, more overarching research questions. The working group is rated as 'very good'.

WG Krutmann: Environmentally induced skin ageing

[5.2 FTE, of which 3.4 FTE research and scientific services staff, and 1.8 FTE service staff]

This working group, which is led by the scientific manager, conducts outstanding molecular research on environmental impacts on skin health, which resonates throughout the institute in an extremely inspirational manner. The group has for many years been greatly successful at integrating innovative research approaches into the scope of its work, most recently, for instance, in research on susceptible phenotypes. For this purpose, it has developed partnerships in an excellent, strategic manner with other internal and external units that bring in complementary expertise, e.g. from the field of epidemiology.

Among the numerous impressive research results that have been published in outstanding publications, highlights include the characterisation of the *Xeroderma pigmentosum* A (XPA) protein and the development of the Düsseldorf Pollution Patch Test, which can assess the effects of traffic-related air pollution on the skin *in vivo*. The working group constantly secures impressive levels of third-party funding from a broad range of funding organisations, and coordinates the DFG Research Unit 5489, which was recently approved. The working group is rated as 'excellent'.

WG von Mikecz: Environmental noxae and cell nucleus

[3.8 FTE, of which 2.7 FTE research and scientific services staff, 0.7 FTE doctoral candidates, and 0.5 FTE service staff]

This working group studies the impact of nanoparticles on the model organism *C. elegans*. It pursues overarching research questions from the fields of nanotoxicology and epigenetics in a highly convincing manner. Its research on worms from different age groups investigates differences in age-related susceptibility to environmental stressors. It is very good to see that the small working group has been consolidated since the last evaluation and now has a critical mass to pursue its important questions in an effective manner and with sufficient breadth.

The research results achieved by the group, which are based on an outstanding genetically modified *C. elegans* model, are very good and highly innovative, partly because of the integration of new technological approaches. The research could be improved still further through a more systematic consideration of biomarkers and genetic research questions. In view of its size, which is still small, the group achieves a very good publication output and level of third-party funding. The group's specific research profile offers very high potential for providing advice to policymakers and society. The working group is rated as 'very good to excellent'.

WG Schikowski: Environmental epidemiology of lung, brain and skin ageing

[8.8 FTE, of which 2.0 FTE research and scientific services staff, 1.3 FTE doctoral candidates, and 5.5 FTE service staff]

The Schikowski group, which focuses on air pollution, conducts very good research using established epidemiological methods. The expertise in this group is of overarching importance for the IUF as a whole, since it enables molecular and cell biology findings to be tested on population studies, and vice versa. Accordingly, the Schikowski working group is closely linked to the other working groups.

Since being promoted to a regular working group in 2016, following the departure of an earlier working group on environmental epidemiology, it has been the only epidemiological unit of the IUF. Hence, considering its small size, it is involved in a large number of cohort studies. It is responsible for the cohorts of the IUF (SALIA, GINIplus and the IUF part of the German National Cohort, NAKO) and is also involved in large studies in China, India and Japan. Moreover, it is a cornerstone of the institute's data science concept. It will benefit considerably from the expansion of biostatistical and modelling expertise at the IUF. The working group is rated as 'very good'.

WG Schins: Particles, inflammation and genome integrity

[4.7 FTE, of which 3.0 FTE research and scientific services staff, 0.7 FTE doctoral candidates, and 1.0 FTE service staff]

The Schins working group studies the toxicity of inhaled and ingested particles. At cellular and molecular level it focuses on inflammation in the pathogenesis of particle-induced diseases. The group's aim is to develop and make available knowledge about particle toxicology processes for transfer to regulatory authorities, without developing toxicology tests itself. It has a close-knit international network.

Over the years, this well-respected working group has been dealing with ever smaller particles, particularly mineral dust, and has a very good publication output in this area. One notable finding relates to the impact of Saharan dust on the NLRP3 inflammasome. For the continuing success of this group, it will be important to build on these individually successful research projects and move towards studying bigger, overarching issues. DFG-funded projects offer a very good opportunity for this and should be applied for, as was recommended before. The working group is rated as 'very good'.

Core unit Rossi: Genome engineering and model development (GEMD)

This core unit has been developed since 2018 with additional institutional funds from the federal and *Länder* governments, as recommended during the last evaluation. An excellent scientist has been recruited to run it, who has established the group and defined its profile. It performs top-quality work and is extremely important for the IUF's research, particularly because it produces large numbers of top-quality genetically modified stem cells. Its further development is of key strategic interest for the institute.

The Scientific Advisory Board suggested giving the core unit leader the opportunity to develop a research programme alongside the unit's service tasks. He was subsequently able

to secure a DFG project. The review board supports this move towards greater freedom, in view also of the scientific development of the extremely qualified leader, so as to be able to keep him at the IUF in the long term. It therefore advises the institute's leaders to keep a close eye on how this unit can achieve a balance in the long term between the indispensable services it provides to the institute and its own scientific research areas. The GEMD core unit is rated as 'excellent'.

Core unit Schikowski: Computational exposure assessment (CEA)

The CEA core unit was established from 2020 onwards with additional institutional funds from the federal and *Länder* governments (€280,000 p.a.), which were added to the core budget in 2022. The CEA's mission is to develop models for small-scale exposure assessment in metropolitan areas, for example in India. The startup phase of this core unit is not yet complete, partly because of unforeseen staff turnover, which means that it is currently understaffed with fewer than one FTE researcher. It is currently being led by a working group leader, alongside her other tasks. In order for the unit to be able to work on its very promising tasks, the startup phase must be completed quickly. In particular, the planned coordinator position needs to be filled soon at an internationally competitive level.

8. Handling of recommendations of the last external evaluation

The IUF successfully addressed most of the recommendations that were made by the Leibniz Association Senate in 2017 (see status report, p. A-21 ff.). Construction of the urgently needed new building is now due to start in 2024. As before, the IUF should strive to acquire junior research groups with third-party funding.

Appendix

1. Review board

Chair (Member of the Leibniz Senate Evaluation Committee)

Ulf **Müller-Ladner**	Department of Rheumatology and Clinical Immunology, Justus-Liebig University Giessen, Campus Kerckhoff Clinic, Bad Nauheim

Deputy Chair (Member of the Leibniz Senate Evaluation Committee)

Nicola **Fohrer**	Department of Hydrology and Water Resources Management, Kiel University

Reviewers

Ilaria **Bellantuono**	The Healthy Lifespan Institute, University of Sheffield (UK)
Emanuela **Corsini**	Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano (Italy)
Martin **Göttlicher**	Helmholtz Munich, German Research Center for Environmental Health
Ulrike **Köhl**	Fraunhofer Institute for Cell Therapy and Immunology IZI, Leipzig
Annette **Kopp-Schneider**	Division of Biostatistics, German Cancer Research Center (DKFZ), Heidelberg
Carien **Niessen**	Department of Cell Biology of the Skin, University of Cologne
Karin **Scharffetter-Kochanek**	Clinic of Dermatology and Allergology, Ulm University Medical Center
Sylvain **Sebert**	Center for Life Course Health Research, University of Oulu (Finland)

Representative of the federal government

Alissa **Winter**	Federal Ministry of Education and Research, Bonn

Representative of the Länder *governments*

no participation

30 June 2023

Annex C: Statement of the Institution on the Evaluation Report

Leibniz Research Institute for Environmental Medicine, Düsseldorf (IUF)

Das *IUF – Leibniz-Institut für umweltmedizinische Forschung* dankt den Mitgliedern der Bewertungsgruppe und den Mitarbeiterinnen und Mitarbeitern des Referats Evaluierung der Leibniz-Gemeinschaft sehr herzlich für die sehr fundierte, konstruktive und äußerst engagierte Arbeit während des Evaluierungsprozesses.

Die Geschäftsführung des IUF und die Arbeitsgruppenleiter*innen haben den Bewertungsbericht gelesen und diskutiert. Außerdem wurde der Bericht dem Wissenschaftlichen Beirat und dem Aufsichtsrat zur Kenntnis gegeben.

Das Institut sieht den Bewertungsbericht als fair und treffend an. Wir freuen uns sehr über die positive Beurteilung unserer Leistungen und unserer aktuellen und zukünftigen Forschungsstrategie.

Das IUF dankt seiner Belegschaft für die erbrachten Leistungen. Wir danken zudem ausdrücklich dem Wissenschaftlichen Beirat und dem Aufsichtsrat des IUF für ihr außerordentliches Engagement.

Wir danken dem Bund und dem Land Nordrhein-Westfalen für die Bereitstellung der notwendigen Mittel zur Errichtung eines neuen Forschungsgebäudes für unser Institut.