

Risk Assessment of Toxic and Immunomodulatory Agents (RATIA)

Mission statement

The program is designed to improve the scientific basis for assessment of risk to humans, animals and ecosystems from exposure to potentially harmful agents in the environment, in occupational settings, through vaccination, and through the food chain.

Program outline

Aims of the program

The program Risk Assessment of Toxic and Immunomodulatory Agents (RATIA) aims at the development and further improvement of the scientific basis for assessment of risks (to human, animal and ecosystem health) of exposure to environmental agents.

Research focus

Specifically, the RATIA program focuses on:

- veterinary public health issues related to food safety, and allergies to domestic, laboratory and farm animals
- human and environmental health issues such as risks of exposure to biological, physical and chemical agents, and vaccines
- occupational health issues such as risks to health of workers in concentrated animal feeding
- operations (CAFOs) and the animal feed industry, and veterinarians
- ecosystem health issues such as endocrine disruption effects of various contaminants on animal wildlife

The interfaculty Institute for Risk Assessment Sciences (IRAS) is supported by the veterinary and medical faculties and the complete research program of IRAS is therefore included in the RATIA program. For this reason, inevitably, part of the research will not have a veterinary focus only, but other parts of the research program fit well in the Academic Biomedical Cluster (ABC) and research program of the medical faculty. In addition, the Department of Immunology from the Veterinary Faculty plays an essential role in research line three from the RATIA program.

Program design

The RATIA program has four research lines, which are essentially the pillars of the program:

1. Exposure assessment & control
2. Mechanism of action and dose-response assessment
3. Environment and host response modulation
4. Human population health effect studies

The RATIA program research lines all feed directly into improvement of risk assessments. For three research lines (Exposure assessment & control, Mechanism of action and dose-response assessment, Human population effect studies) this is self-explanatory. Environment and host response modulation, focuses on specific immunomodulatory mechanisms, which plays a crucial role in determining effects of agents that are of specific interest in the RATIA program. This research includes agents implicated in auto-immune and allergic diseases, and anti-microbial vaccines, which are important from a public health point of view. This clearly distinguishes the 'immunology line' within the RATIA program from the Strategic Infection Biology (SIB) Program in which exposure to infectious agents, infection and resulting infectious diseases are the main interest. In the latter program, research focuses on modulation of the risk of developing (chronic inflammatory) disease(s) by exposure to microbial agents, including infectious and non-infectious agents. In the case of the RATIA program the human and environmental risks associated with the occurrence of (non) infectious micro-organisms in food of animal origin and waste produced by

the animal production process are an important focus of RATIA and is of course highly relevant for (inter)national veterinary public health research. As can be seen from the list of ongoing projects

in RATIA a variety of studies are ongoing or will be started in the near future.

The common risk assessment 'paradigm' distinguishes hazard assessment, exposure assessment, dose-response assessments, risk characterisation and management as essential elements of the risk assessment process.

Hazard assessment focuses on answering the question whether a particular agent has the potency to do harm (to human, animal and ecosystem health). Toxicology is an important discipline to answer this question, while in some cases input comes from epidemiological observations.

Exposure assessment contributes to risk assessment through precise quantification of the exposure level to the target species (human or animal) and exposure distributions in populations.

In order to properly assess the exposure this includes development of measurement techniques, measurement strategies and exposure models. In many situations the actual quantification of the (distribution of) exposure to an agent should be considered the first step in a realistic risk assessment. Dose- response assessment is the domain of both toxicology and epidemiology, focusing on laboratory experiments and (observational) population studies respectively. Risk

characterization integrates the information from hazard assessment, exposure assessment and dose-response assessment into a quantitative characterization of the risks (probability of developing a negative effect) operating in specified populations or the impact (numbers of individuals affected in an exposed population). Within the research line 'environment and host modulation' research is focussed on the immune system as an unique sensitive early warning system for any loss of host self-integrity caused by endogenous or exogenous factors. This research line aims at studying aspects of immunity and immune mediated chronic diseases, In addition, the immune system has an array of devices (receptors and cells) to monitor the presence of exogenous factors that may have a deleterious impact on host self-integrity. For these reasons this program will exploit these aspects of the immune system as the read-out for risk assessment. A specific topic of interest, are indicators of a modulated (by exogenous factors) immunological status. Logically, research in the nature of this modulated status is connected to research aimed at manipulating such modulated status.

Ratia Research line 1 Exposure assessment & control

Line coordinator – Prof.dr.ir. Bert Brunekreef,
Institute for Risk Assessment Sciences (IRAS)

Any organism is exposed continuously to natural and anthropogenic agents, which threaten its health and well-being. The projects within the 'Exposure assessment & control' research line, therefore, focus on the identification of physical and chemical factors in the environment, whether being occupational, domestic or in the biosphere. This exposure assessment will provide the information that is necessary to control or reduce the presence of these agents to protect human and environmental health.

Besides the data provided by chemical analytical techniques it is also necessary to understand the routes of contamination. To obtain this knowledge specific routes of transport and their interaction and the development of (mathematical) models that describe the processes, which underlie the exposure, and contamination of a specific environment or matrix with a specific agent have to be studied. Such models will fuel new sampling and analysis strategies, which are crucial to control and finally to manage the respective factor. Obviously, the development of these models depends initially on analytical data. In addition, these models need to be validated in order to be accepted by regulatory authorities and risk managers. In view of the topic of this research line – exposure assessment and control- it is obvious that advanced, sophisticated and adequate-for-the-purpose analytical or diagnostic assays will be essential tools and will consequently be given much attention in terms of development and design.

Another important research issue within this research line is the identification of emerging threats for humans, life stock and the environment. Thus, the methodological strategies used and developed in this research line are not only used to provide authorities, industry or other

professionals possibilities to monitor possible adverse external factors, but are also meant to be tools to identify and monitor new developing risks.

1) Development of new techniques for exposure assessment

The increasing demand for quantitative exposure data in veterinary , environmental and occupational epidemiology has led to an urgent need for improved exposure assessment tools, which can be applied in both on going as well as multi-centre epidemiological studies. The newly developed methods within this research line should be, and are especially used to quantify the concentrations of chemical contaminants in relation to exposure and risks for humans and environmental biota. In view of the special position of the Faculty of Veterinary Medicine in our country special emphasis is on human exposure through food of animal origin and the possible risk associated with the presence of chemical contaminants, hormones and pathogenic microorganisms. In addition, environmental and occupational exposure to chemical agents (e.g. contaminants, pesticides and hormones) are included as research topics, as are effects on environmental biota (e.g. wildlife and fish) and professional groups like veterinarians and farmers, which are considered to be part of the research domain of the Faculty of Veterinary Medicine. Several projects are done within the coming time period with focussing on bioavailability of chemical contaminants in the environment. This aspect of bioavailability plays nowadays a key role in ecological and human risk assessment. Quantifying the risk of pathogenic microorganisms in human food of animal origin is a prime focus of the veterinary public health part in this program and several projects including occurrence of *S. aureus*, *E. coli* and *Campylobacter* sp. are included in this program.

Included in this research line are also some new innovative cost and time effective approaches based on new detection technologies such as advanced biosensors, transcriptomics. The new techniques will enable faster screening of feed and husbandry animals with respect to the presence of growth promoting anabolics, parasitic infections and pathogenic micro-organisms. It is also expected that the development and use of these new techniques will also strengthen further the earning capacity in the years to come for the RATIA program.

2) new methods for occupational exposure and control techniques

So far very little research interest has been given to aspects of occupational hygiene and epidemiology for professional groups that are specifically related to the activities of the Faculty of Veterinary Medicine. These occupational groups include among others veterinarians, hospital personnel and farmers working with production animals. An important study in this respect is the 'Veterinarians Health Study' that will be performed the coming years at the Veterinary Faculty among students and will provide essential and unique information about the health risks associate with the veterinarian profession. In addition, a range of other studies among occupational groups in either agricultural or industrial settings will be done.

(New) hazards in the (work) environment continue to evolve and new technologies and applications can lead to physical, biological, and chemical exposures that were previously non-existent for the populations under consideration. New projects have been or will started in relation to exposures and possible risks of hospital workers associated with the use of antineoplastic agents and high magnetic fields and optical radiation. We also participate in two NWO/ ZonMw research programs on exposure to and health risks of electromagnetic fields These type of research projects will clearly be a collaboration between this research line and lines 2 and 4 as mechanisms of action and related health effects and risks are often unknown.

3) Model development

Much quantitative epidemiological information has been obtained during the last decades with ever improving analytical techniques. Within this research line the application and development of statistical and mathematical models will be continued and much of the research activities focus on air quality and contribute to improved risk assessment for both humans.

As can be seen from the overview of projects within this research line much of the ongoing and

future activities concentrates on e.g. health effects of fine particles and cardiovascular and respiratory effects by air pollution in a broader sense. Within these projects geographical and spatial variation receives significant attention. In view of the observed health effects related to air pollution it is obvious that this type will be done in close collaboration with activities in line 4 (human population effect studies) and increasingly, 2 (immunotoxicological mechanisms). A special focus is validation of GIS based exposure classifications against personal exposure measurements including development of measurement error corrections for exposure response relationships.

Coherence of the research line

The results that are obtained in the three topics above that form this research line will be highly useful for epidemiologists, toxicologists, environmental and occupational hygienists and immunologists and are also expected to provide new research input. The results coming out of this research line furthermore provide significant support for the other research lines 'Mechanism of action and dose-response assessment', 'Environment and host response modulation' and 'Human population health effect studies' within the research program of RATIA.

RATIA Research line 2: mechanism of action and dose-respons assessment

Line coordinator – Prof.dr. Martin van den Berg

IRAS, Dept. Pharmacology, and Dept. of Infectious Diseases and Immunology (I&I)

This research line covers part of the risk assessment area in which the availability and the dose of toxic substances are studied in relation to their potential to induce adverse effects.

Specific aims are to assess how the bioavailability and the distribution among environmental compartments of chemicals may relate to toxic hazard for the natural environment. The sorption to soil and sediments, tissue partition and internal dose are measured and modelled in order to understand the availability and kinetics of toxic substances within organisms and to predict toxic hazard. To predict the availability of external and internal exposure to toxic substances for the organism *in vivo*, novel *in vitro* methods, sampling techniques and models are developed. In parallel, toxic effects are studied to reveal the biological mechanisms of action of toxic substances (food-related products, health products, drugs and environmental contaminants) on the immune, the neural and the endocrine system. Receptor interactions and the consequences for cellular signalling and cellular communication are investigated to develop an understanding of cellular and molecular toxic, immunological and endocrine mechanisms. In the period 2006 -2011 this research line was strengthened strong collaboration with the RIVM in the fields of developmental and reproductive toxicology and human clinical toxicology. Furthermore research on the development of alternatives for animal models will be strengthened by more intense collaboration with the RIVM. In practice this means that during the review period many projects have been obtained in the field of endocrine, neurotoxicology, immunotoxicology and endocrine toxicology. The introduction of and RIVM chair in developmental and reproductive toxicology as well as an endowed chair for alternatives in animal experiments also allows more interactions between the RATIA program and other research programs from the veterinary faculty. More specific topics in this research line are:

1) Xenobiotic-induced effects on immunotoxicity

Research on mechanisms of adverse immune effects as result of exposure to xenobiotics, such as pharmaceuticals, food allergens and air pollutants has been an important aspect of this research line. The induction of allergic or autoimmune responses, through pro-inflammatory or immunosensitizing responses to toxic challenges is investigated, and particular attention is given to in the role of mucosal barriers of the intestinal tract and lungs. Focus of this research remains on the role of the innate and regulatory components of the immune system. Data on food and drug allergies are used to improve predictive models to assess potential hazard of foods or drugs to induce allergy, but also to design therapeutic venues. Studies with regard to airway allergy will offer increased knowledge-based simple straightforward models to assess immunostimulatory potential of air pollutants and nanoparticles. The expected outcomes with respect to immunotoxic effects described above are going to be used to develop or improve test models and strategies to estimate the immunotoxic risks of exposure to xenobiotics, but also to design immunotherapies. It is also foreseen that this part of the research will also connect more and more to the human biomedical research with respect to side effects of pharmaceuticals.

2) xenobiotic-induced effects on endocrine toxicity

Within this topic, research will continue to focuses on the molecular endocrine mechanisms underlying the toxicity elicited by exposure to xenobiotics, These compounds comprises a broad range of compounds ranging from synthetic environmental pollutants to natural food-borne compounds. Many *in vitro* bioassays are in use and we will continue to use both cell lines as well as primary cell cultures with human tissues obtained from hospitals nearby. The focus of these studies is on the interference of xenobiotics with biological and endocrine responses, such as (steroidogenic) gene expression, enzyme activities and interaction with (steroid hormone) receptors. Relevance of these interferences in the prevention or development of hormone-dependent tumours, such as breast and prostate cancer are part of ongoing studies in the period 2006-2011. As chemoprevention of tumour formation by e.g. natural compounds of structural derived congeners is getting increased attention from toxicologists this line of research is still

expected to grow in the coming years. This type of research also offers collaborating possibilities with both the biomedical field as well as pharmaceutical sciences. In addition, the possibility is studied to which extent the occurrence of specific endocrine related tumours in companion animals can serve as a model for the human situation. This approach should allow more interaction with other research programs of the Veterinary Faculty in the years to come. Another research area within RATIA that will strengthen links with other research activities with the Veterinary Faculty is research on mycotoxins done by the Pharmacology Group. These natural toxins are among the most prevalent contaminants of feed materials and certain food commodities. The research is focussed on the understanding of the molecular mechanisms involved in the adverse endocrinological and immuno-modulatory effects of these compounds. The obtained results are applicable to risk characterization in humans as well as farm animals, and provide a rationale for intervention strategies.

3) xenobiotic-induced effects on neurotoxicity

Mechanism of neurotoxicity of environmental toxicants (e.g. pesticides, solvents, flame retardants), drugs, radiation and endogenous substances has been a major focus of this part of the research line 2 within the period 2006-2011. In this respect the important research efforts will include membrane signalling through membrane receptors and ion channels, and on cellular communication through exocytosis as in the past. Advanced electrophysiological and imaging neurochemical techniques remain the principle tools for these type of studies. Like the present ongoing research projects, the development and improvement of in vitro models of cells of the neural and immune systems is going a significant aspect of the present and near future scientific activities within this field. Besides in vitro studies focusing on neurotransmission and human neuroreceptors, there will be further use of in vivo models, e.g. neurospheres, because of the suspected developmental neurotoxic properties of various chemical contaminants. New insights into neurotoxic mechanism also have revealed that these can be closely associated or connected with endocrine or immunological mechanisms. Thus, collaboration with the endocrine and immunotoxicology groups is a distinct possibility for the future of this research group.

4) xenobiotic-induced effects on the environment

The research in this topic is directed towards a better understanding of the exposure and kinetics of chemicals in relation to effects on human health and ecosystems. In the coming time period research remains focused on studying mechanisms of sorption of organic contaminants to sediment and soil and the effects of sorption on bioavailability, bioaccumulation and toxic hazard for the natural environment. These aspects continue to an important aspect for risk assessment of xenobiotics as a major uncertainty is often coming from this. Part of this type of research is also done in the research line 1 (Exposure assessment) where these aspects are also important for human and veterinary orientated studies. In view of the fact that the Department of Biology of the Beta-Faculty has withdrawn its support to IRAS in 2010 due to budgetary reasons, a shift from more ecological orientated research towards veterinary and human health issues is expected in this research line. The excellent analytical laboratory capacities need to be more focussed on topics that are more relevant for the veterinary faculty, as well as public health. The environmental and food derived exposure to complex mixtures also is an important issue for risk assessment in the years to come. Complex mixtures effects will be determined using innovative extraction techniques combined with in vitro assays representing a specific toxicological mechanism of action.

Coherence of the research line

The goal of the this research line is to support and facilitate risk assessment by contributing basic knowledge on the (bio) availability and hazard of toxic substances, primarily by developing novel concepts and models to enhance the understanding of mechanisms of toxicity in relation to the dose to which the organism is exposed. As such, the toxicology research is complementary to the other research lines in the program "Immunity and Risk Assessment". Moreover, aspects of this research line offer possibilities to exchange fundamental en technical know-how with the programs

“Strategic Infection Biology” and, Biology of Reproductive Cells (BRC) in particular with respect to, respectively, immuno-modulation and mechanism of action of endocrine disrupting chemicals.

RATIA Research line 3: Environment and host response modulation

Line coordinator: Prof. dr. Willem van Eden

Dept. of I&I and IRAS

This research line has its focus on immune modulation in relation to chronic immune - mediated diseases, such as allergies and autoimmune diseases. In this research line we study immunological mechanisms in relation to food and immune-modulating environmental agents, such as microbial components (including vaccines), probiotics, adjuvants, chemical compounds, drugs and aeroallergens such as house-dust mites and pollens. These studies are aimed at uncovering causal factors, potential risk factors of disease and mechanisms. In addition the studies aim at the development of novel therapies for animals and have ramifications – in collaboration with the UMCU - to development of immunological interventions in human diseases. For this, intense and long-standing collaborations exist between human and animal oriented research groups in relation to (juvenile) rheumatoid arthritis and allergies. The fact that the research in this research line has implications for both veterinary and human medicine gives the RATIA program a very good link to the biomedical research at the Utrecht University.

The immunoregulatory events associated with mucosal tolerance and immunological regulation through T cells are central themes in the projects of this research line.

The research of this line is carried out, besides in various in vitro systems, also in spontaneous and experimental disease models. Food allergies and atopic dermatitis in cats and dogs, asthma in cats and colitis (inflammatory bowel disease) in dogs are the natural disease models that are being studied. Experimental models include, partly unique, models of allergic asthma, arthritis and inflammatory bowel disease in mice and rats.

A unique aspect of this program is that animals are both target species and model systems for development of innovative interventions that can be use for the human situation.

1) (Environmental) stress response

The stress responses in cells and in particular the induction of stress proteins or heat shock proteins and xenobiotics are studied and will continue to be an important research topic in the upcoming time period. Specific attention will be given in the near future on the role of HSPs in experimental colitis in which the dog is playing an important role. The role of immunomodulation in the occurrence of atopic dermatitis and food allergies will also be studied in the dog the coming years. In addition, the role of proteoglycane (PG) specific T cells as IL 10 Trojan Horses is being studied in more detail and finalized in the coming years. The immunomodulatory aspects of such stress responses are studied in vitro and in in vivo disease model systems. For bacterial heat shock proteins their immunomodulatory mechanisms will be studied in various in vitro and in vivo model systems. Studies are also going to include interactions between dendritic cell and T cells, next to the oral tolerance with HSP and PG in the PG arthritis model. The ongoing and planned research for several projects mentioned above will be done in close collaboration with the Department of Companion Animals and IRAS (immunotoxicology) With respect to modulation by xenobiotics of mucosal immune responses, pharmaceuticals, food-derived and microbial components will play a significant role. These groups of compounds are going to be studied in relation to food allergy, drug allergy respiratory allergy, and inflammation. The major focus is and will be on revealing mechanisms of innate and adaptive immunoregulation. It is expected that results from these ongoing and future studies will contribute to the use and development of immunotherapies and/or predictive assays of immunotoxicity

2) Monitoring immune status

Novel tools are developed in this particular topic for the measurement of the immune status in relation to vaccines and environmental agent exposures. Assays which will be developed in in

vitro systems and ex vivo systems are aimed to collect and capture antigen specific T and B cells. These assays will furthermore be used to measure their functional phenotypes and the cytokines produced. Another significant part of this research topic is the application of these techniques to monitor the immune status in the Veterinarians Health Study performed at the Veterinary Faculty of the UU. This research project is also a collaboration between the RATIA research lines 1 and 4. In addition, the techniques for measurement of the immune status will also be used to determine infections with pathogenic micro-organisms in the human food chain.

3) Immunopathogenesis and therapeutic immune-modulation of inflammatory diseases

Immunomodulatory approaches such as novel principles for antigen specific immuno-therapies are developed in this research topic. It will be done within the framework of existing relationships between the Faculty of Veterinary Medicine and the Medical Faculty (UMC Utrecht) of our university for translational research. In addition, extensions to immunotherapies of companion animals are part of the strategies to develop such novel principles, which are of direct use in clinical practice in the Faculty of Veterinary Medicine.

Coherence of the research line

Chronic immune-mediated diseases are an increasing problem in the industrialized Western world. The driving factors in this are likely to be of a complex nature and may involve genetic factors, allergen exposure, infectious agents such as staphylococci and round worms, vaccinations, etcetera. The research line "Environment and host response modulation" especially complements well the research lines "Mechanism of action and dose response assessment" (2) and "Human population effect studies" (4) in the program "Risk Assessment of Toxic and Immunomodulatory Agents (RATIA)" and in addition complements clearly the research activities from the research program "Strategic Infection Biology".

RATIA Researchline 4: Human population effect studies

Line coordinator: Prof. dr. Dick Heederik
IRAS and Dept. of I&I

This research line focuses on relations between exposure to biological and chemical agents and resulting health effects in human populations. This is an interfaculty program, in which close collaboration exists with research groups within the medical faculty.

Biological agents include bacterial toxins such as endotoxins and allergens. As far as knowledge reaches at this moment the risk of developing chronic diseases is modified by exposure to microbial agents and toxins. In view of the special position at the Faculty of Veterinary Medicine specific emphasis is now given more to interrelationships between animals and humans, their resulting exposures and possible adverse health effects. Animals can be seen as a reservoir of micro-organisms, which can result in human exposure to toxins and allergens in the domestic and occupational environment. This can result in a-specific inflammatory and specific allergic responses in humans. Exposure to infectious agents and the resulting infections and diseases through the work environment or the food chain are also included in this research line, but are clearly topics of interest in the Infection Biology program (SIB). Thus, this area of research presents a good opportunity for inter-program collaboration between RATIA and SIB.

1) Modulation of allergic responses by microbial agents in humans

Research will continue with respect to the role of microbial agents with regard to modulation of responses to allergens and expression of exposure on the level of human populations. Population studies among veterinarians, specific groups of agricultural workers, general population adults and children, cross-sectional and longitudinal studies are on going to monitor the prevalence and incidence of especially allergic responses but also other endpoints, including cancer. There is for example specific interest in the relationship between microbial exposure, lung cancer and non-Hodgkin lymphoma and associations are explored in large scale epidemiological studies like the international collaborative EPIC study. In most of the studies

in this topic area inhalatory allergen and microbial exposure will be measured and information on confounding variables is collected. The ongoing and future health effect studies will include questionnaires, spirometry and bronchial hyper-responsiveness. All these studies include a bio-banking component and this approach clearly facilitates application of approaches such as transcriptomics that remain of increasing importance. The use of genomics techniques is already done within UU collaborations and participation in EU programs. In the coming time period special interest will be given to development of measurement techniques to characterize MAMP environmental exposure (other than endotoxin), application of these measures techniques in various epidemiological surveys and evaluation of variability and possibly reversal of specific sensitisation in humans influenced by MAMP exposure

2) Health effects by man-made chemicals and pharmaceutical products

Exposures to fine particulate matter and polycyclic aromatic mixtures from (incomplete) combustion processes and those related to veterinary and agricultural practices (pesticides, disinfectants and biocides, pharmaceuticals) may result in health risks for certain populations. In view of the wide spread air pollution and common use of these xenobiotics epidemiological research in these areas will remain an important aspect of this part of the RATIA programs in the years to come.

Data for these studies comes from longitudinal long term epidemiological (mortality or (cancer) incidence) studies coordinated by external groups, in which the environmental or occupational exposure assessment is incorporated to facilitate exposure response modelling.

With respect to research on chemical exposures in specific human populations aspects like the use of Geographic Information Systems and activity pattern studies in combination with routine exposure data remain important. Furthermore, the development and use of biochemical or molecular biomarkers of exposure will be of continuing interest in the ongoing and future projects to determine individual susceptibility

3) Risk and health impact assessment

At present and in the coming years epidemiological evidence and information on exposure in human populations is going to be used more and more to perform risk assessment and evaluation of the impact of exposure to chemical and biological agents in population (health impact assessment). Results from this type of studies are expected to predict better the probabilities or numbers of diseased individuals or other indicators of health impact (lost quality of life, or quality of life adjusted life expectancy) in human populations. To strengthen this field, a stronger relationship with the National Health Institute of Public Health and Environmental Protection (RIVM) has been built up during the last years. To perform these studies adequately there is a need for the use and development of complex mathematical models that describe the complex interactions between different exposure variables or confounding variables. These approaches are expected to be applied more and more in planning of preventive health strategies. Thus research on the development and use of these new mathematical/statistical models is becoming increasingly important and will be done in many of the studies performed in this research line.

Coherence of the research line

This research lines makes use of observational epidemiological approaches. Results obtained in the first two lines will be applied in the last one, risk and health impact assessment. Some overlap exists between the first two topics, especially when interactions between biological agents and chemical agents are expected to play a role and specific hypothesis regarding interactions will be explored and tested. Topic one of this line is closely related to the more mechanistically oriented research line 3 on 'Environmental exposure and host responses'. The relevance of mechanistic insights that will become available in line 3 will be evaluation in human population studies. Topic two has a similar relationship to the Toxicology line.

Program organization

The program combines research efforts from the interfaculty Institute for Risk Assessment

Sciences (IRAS) and from the Department of Infectious Diseases and Immunology (I&I). The program is presently embedded in the university research focus area 'Infection and Immunity' with links to the research focus area 'Epidemiology'.

RATIA contact

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