On-going Strategic Research RIVM (SOR)
2007-2010

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1 Preface

This report presents the summaries of the project proposals selected for the Strategic Research Program (Dutch abbreviation SOR) of the National Institute for Public Health and the Environment. The Strategic Research Program passes through a four-year cycle. The projects presented are selected for the period 2007-2010. The selection of the projects was completed in September 2006.

1.1 Aim of the Strategic Research Program
The aim of the Strategic Research Program is to safeguard the scientific continuity of RIVM either by filling knowledge gaps, or by anticipating on new or future developments to reinforce the institute’s national and international position.
According to this aim, six strategic themes were formulated:
- Risk Assessment, Perception, and Consumer Behaviour and Understanding
- Emergency Response Functions and Safety
- Infectious Diseases
- Chronic Diseases, Intervention and Lifestyle
- Medicines and Functional Foods
- Environmental Quality and Health

1.2 Criteria for selection
The submitted proposals had to fit into one of the strategic themes. The proposals were evaluated based on a number of criteria in order to be eligible for financing through SOR:
- Research questions/approach
- The proposal has realistic goals and is clearly formulated
- Transparency on potential critical moments within the project
- Clear description of the expected results
- The project facilitates new national and/or international collaborations

Strategic or innovative nature
- It addresses key tasks of RIVM and fits within one of the six strategic themes
- The project is needed to assure continuity in the field of research/knowledge for RIVM
- The project anticipates on new developments, with a high potential of generating new assignments
- The project contributes to the (inter)national scientific position of RIVM
- The project addresses serious threatening knowledge gaps

1.3 In this report
The following chapters each comprise a strategic theme. After a short description of the theme the projects are listed. Each accepted project proposal is summarized. Abbreviations behind the name of the project leader indicate
organizational units within RIVM. Total costs are provisional estimated lifetime costs (2007-2010) of the projects. Some projects will continue after this period, these costs are not included.
This theme represents a key competence of RIVM, which is important for all research sectors. Working on this theme also implies strong opportunities for intersectional cooperation. Risk assessment, perception & consumer behaviour are relevant research subjects, appropriate for the major RIVM knowledge areas such as source of threat, effect studies, system functions and effective interventions.

Projects

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2.1 S/260196 Effective Use Performance Indicators, Dr. M.J. van den Berg

2.1.1 Motivation

In the Netherlands, a consensus is emerging that there is a strong need for performance measurement in health care. There is increasing political pressure to make health care professionals and institutions perform better by developing and implementing quality indicators and performance schemes for both external accountability and transparency and internal quality improvement. The RIVM has been working on the issue of quality of care for many years. We developed quality indicators for several medical specialist professions. We are now facing a new challenge in the research on quality indicators: ‘can we improve the quality of care by using quality indicators and in which way should we apply indicators to achieve optimal quality improvement at the level of health care professionals?’ These questions are essential to make the future development and implementation of quality indicators worth the effort. In this project, evidence-based indicators have to be put into practice. At present no clear information is available on the effect of indicators and how we should implement them to optimize effect. This knowledge needs further development.

2.1.2 Aim of the project

General aim is to study how health care professionals can use performance/quality indicators to improve the quality of care provided to their patients in the hospital. Specific aims:

- To select sets of quality indicators for hospital care by medical specialists, in the domains of clinical practise, governance, and patient safety.
- To explore strategies for effective use and implementation of quality indicators for medical professionals in the hospital.
- To adopt and/or develop strategies for the effective use of quality indicators by medical professionals in the hospital, applicable for Dutch hospitals, with special focus on information feedback and embedding of indicators in management systems.
- To develop methods (qualitative and quantitative) to measure quality improvement in clinical practise, in response to the use of quality indicators.
- To test the effectiveness of the developed strategies on the quality of care in selected areas in the hospital.

2.1.3 Strategic and innovative aspects

In the development of quality indicators for health care we can distinguish several phases. In the Netherlands we are at the stage in which indicators for health care have been developed, but not yet firmly implemented and tested on

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1 The study will be carried out in close collaboration with Tilburg University (Tranzo). Tranzo is specialized in implementation/change strategies in care settings, with regards to infrastructure (e.g. cooperation with hospitals) and knowledge. This project relates to two other RIVM-research studies on performance measurement in health care. We will be in close collaboration with these projects.
their effect. At this stage there is a great need to make effective use of quality indicators. RIVM can develop methods for optimal use of indicators which can also be adopted by other organisations in the implementation of quality improvement. The RIVM has been in a position in previous projects to develop indicators and in this project will make this next step towards its effective use. The RIVM is increasingly involved in projects on monitoring quality of care by using indicators. Also in the new expertise centres at RIVM (e.g. CVB, CIB), indicators will be used for quality management. Therefore, it is important to increase knowledge on the optimal use of indicators at RIVM. This study will contribute to the development of this knowledge.

2.1.4 Planned activities

1. Defining intervention strategies and outcome variables
   a. Selection of indicators. In previous projects at RIVM, we developed sets of indicators for the Intensive care units (ICUs) and obstetric care, in close collaboration with the scientific boards of the professional medical organizations. From these indicators, a selection will be made for those most suitable for implementation. Several criteria will be applied for this selection.
   b. Defining an implementation strategy. We will explore, adopt and/or develop a strategy for implementation of quality indicators. Based on an inventory of strategies used in the Netherlands and abroad, literature search and expert consensus.
   c. Method for measurement of outcome. We will develop a method (qualitative and quantitative) to measure quality improvement, in response to the use of quality indicators. This method will include an in-dept study in the hospitals on the results of working with indicators.

2. Experimental study on the effectiveness of indicator use
   a. Effect of using indicators. Using the developed method for outcome measurement (as mentioned above) we will test if the implementation strategy results in improvements of the quality of care. During an 18-month study, intervention hospitals will be compared to hospitals with usual practice.

2.1.5 Planned products

- PhD-thesis.
- A series (approx. 6) of scientific articles published in peer reviewed scientific journals
- Presentations of study results at national and international conferences.
- Disseminating results via press releases in relevant media or journals.
- An RIVM report on the methodology of the implementation strategy for hospitals and other organizations involved in implementing indicators for health care professionals.
- Assistance in RIVM projects/centers on the effective use of performance/quality indicators.
2.1.6 Foreseen follow-up

The selected strategy for implementation and its effectiveness may determine how quality improvement projects using indicators will be designed. The results of this project may stimulate the use of indicators to improve health care quality and efficiency. The results of this study will be put into practise in future RIVM projects on the monitoring of quality in health care.

2.2 S/270136 GettingBetter.nl, Drs. H.C. Ossebaard

2.2.1 Motivation

The Dutch government promotes ICT in health care and health information. The implementation requires the development of knowledge and capacity to meet informational challenges posed by trends such as the role of the internet, patients’ and citizens’ need for more and better health information, the increasing urgency of patient-safety, the ageing population, or rising health costs. While consumers are increasingly responsible for directing their own health (care), e-information and e-tools needed are not keeping pace. Equally, consumers lack the skills to effectively use them. Therefore the concept of eHealth literacy ("the ability to seek, find, understand, and appraise health information from electronic sources and apply the knowledge gained to addressing or solving a health problem") needs to be addressed exhaustively. In a consumer-centred health care system it is distinctly imperative to fill these gaps, preferably in a scientific mode.

2.2.2 Aim of the project

The aims of the present project are to generate knowledge and skills in the field of applied consumer health informatics; to return on investment by delivering company-wide applicable results germane to (future) informational projects aimed at the general public and to contribute to the development of consumer health informatics and exchange key issues at a European level. Specific objectives are:

- To investigate two major informational issues relevant to societal and technological trends: information behaviour of Dutch citizens and information tools and services for citizens.
- The findings will be accommodated to serve additional public information projects.

2.2.3 Strategic and innovative aspects

The project evolves from the practical and theoretical need for evidence with regard to key questions in a consumer centred health care system. It aims to work on a new science area within the RIVM in cooperation with external

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2 The project is related to other public informational assignments of RIVM e.g. the National Vaccination Program. There are relations to nationals projects (e.g. UMC St. Radboud Nijmegen, University of Twente) and international institutes e.g. the Toronto General Research Institute of the UHN (Canada) or the Bertelsmann Stiftung, Gütersloh (Germany).
experts. The innovative nature is further implied by the current lack of data in a wide range of e-health related issues. A combined and innovative effort to meet these needs could seriously advance current and future public enterprises. The output will be valuable for the institute’s current projects, particularly for her new public assignments and statutory responsibilities, and will thus attract new investors.

2.2.4 Planned activities
1. Processing outcomes of the 2006 pre-study: literature search, preparation, planning the process, theory modelling, reporting.
2. Data collection: online consumer survey, national telephone interview study, laboratory experimentation, semi structured qualitative interviews; data analysis.
3. Reporting and dissemination.

2.2.5 Planned products
- PhD.-theses, international scientific publications
- International conferences
- Manifest transformation of kiesBeter.nl: e.g. methods to identify) information needs, common protocols for transmitting consumer content, practical tools (e.g. to make informed choices on medical matters; self-help and self-management tools).

2.2.6 Foreseen follow-up
Implementation of results and output will enhance (future) RIVM products/projects aimed at informing citizens on public health, nutrition, safety and the environment. It will contribute to public and professional visibility. It will facilitate acquisition of follow-up investment; endorse its national and international position as demonstrated by presence in / organization of relevant scientific and policy forums. The outcomes serve the public interest and the public interest only.

2.3 S/320001 Population-based Biokinetic Modeling, Drs. P. Bos

2.3.1 Motivation
Humans are continuously exposed to chemicals, some of which are beneficial (e.g. nutrients) while others may induce health risks (e.g. contaminants in food). In assessing the health implications of such exposures one often has to rely on data that do not directly relate to the target population and/or to the exposure situation considered. For instance, although many risk assessments concern peak exposures the impact of the height and frequency of peak concentrations on target tissue concentrations and thus on the occurrence of health effects, is largely unknown. Another relevant policy-driven question is how variability in physiological parameters (such as body weight, age, gender, or ethnicity) or temporal changes in population composition (e.g. ageing of the population or ethnic differences) or in physiological characteristics (such as obesity) have to be accounted for in health assessments. The usual approach of dealing with uncertainties is to apply assessment factors which are assumed to be conservative, resulting in human intake values that should be safe. However, in many risk management problems a conservative approach does not suffice. In
addition, it is unclear if the default assessment factors are indeed conservative: they might not be sufficiently protective in some cases, while being overly conservative in others. Similar considerations play an important role when considering the health benefits of nutrients or food supplements.

2.3.2 Aim of the project

The objective of the present project is the development of a generic PBPK-model (=Physiologically-Based Pharmacokinetic model) that will provide insight in how the biokinetics of chemicals depend on chemical-specific characteristics and on biological variability in physiological parameters and that can be used to answer all sorts of generic questions. As a knowledge institute with expertise in (functional) foods, hazard and risk assessment including chemical exposure assessment and (PBPK-)modelling, RIVM has the potential to combine these expertises and develop such a generic PBPK-modelling tool. This model will be adaptable to specific classes of chemicals and will be sufficiently flexible to address a wide variety of chemical- and/or exposure specific situations.

Specific objectives of the project

Objective 1a: Database describing (healthy) human subpopulations of interest in terms of physiological and biokinetic parameters (for instance age, BMI or ethnicity).

Objective 1b: Database describing specific groups or classes of chemicals based on relevant physico-chemical characteristics determining their biokinetics.

Objective 2: A generic PBPK-model to predict the internal dose in (healthy) human (sub)populations following exposure to different classes of chemicals and to compare the associated potential health impact in different subpopulations.

2.3.3 Strategic and innovative aspects

PBPK-modelling has successfully been applied to several high-priority chemicals. However, this type of modelling is data-demanding, and its use is limited to that chemical only. In order to substantiate the support of the majority of policy driven questions, a less detailed and more generic approach is required to address two problems:

1. Repeated/intermittent exposures to peak concentrations.
2. The question what the effect of changes in population. The PBPK-model will be constructed such that once this tool is developed other important topics in health assessments may be addressed as well.

The PBPK-model will be constructed such that once this tool is developed other important topics in health assessments may be addressed as well. Depending on the progress these topics may be incorporated in the present project or in future projects.

2.3.4 Planned activities

Activities during the two-year project include the following steps:

1. A literature search and international research programs will be screened to identify relevant databases and tools to model inter-individual anthropometric and relevant PBPK-models that have a more generic character.
2. Classes of chemicals will be defined predominantly based on various properties (e.g. physicochemical characteristics, slowly or rapidly metabolized) that are important for the fate of a chemical in the human body (absorption, distribution, elimination).
3. A ‘standard’ PBPK-model will be built containing both a rat and a human model. It will be examined which parameters are specific and crucial for these questions.

4. In the generic PBPK model, the values of the parameters are defined for a specific class of chemicals and/or for a specific human subpopulation in terms of ranges of parameters in the PBPK model. In this way, a series of class-specific PBPK-models is defined. Then, these models are used to study the relationship between external and internal dose. A performance assessment will be made.

5. The next step is to further develop the model along two lines. The first line concerns the question what the effect of changes in population composition may have on the health effects induced by a chemical substance and to subsequently quantify these relationships. The second problem concerns exposure to peak concentrations or intakes for which at present no satisfactory risk assessment methodology is available.

6. Organization of a workshop with stakeholders.

2.3.5 Planned products

1. Database on distributions of physiological and biokinetic parameters for human (sub)populations.

2. Database on various parameters relevant for PBPK-modelling for specific chemical classes.

3. Generic PBPK-model that can address a number of generic policy driven questions.

4. Workshop with stakeholders at the end of the project.

5. Knowledge on quantitative relationships between chemical properties, physiological/biological parameters and health effects that will improve health impact assessments.

6. Reports on description of the databases on distributions of physiological and biokinetic parameters and on various parameters relevant for PBPK-modelling for specific chemical classes and on the performance assessment of the generic PBPK-model (go-no-go decision).

7. Publications on the description of the generic model, including the performance assessment; on the health assessment of specific exposure scenarios by the generic model; on the health assessment for different subpopulations by the generic model.

2.3.6 Foreseen follow-up

The database will be valuable for future health assessments, either with or without modelling, and can be used for new assignments. The generic model will be used to answer policy driven questions in the future and will be supportive for health risk and health benefit assessments, especially for the ministries involved in these fields.

2.4 S/320002 Improvement of risk assessment, Dr. M.I. Bakker

2.4.1 Motivation

Recently isoflavones have attracted toxicological attention, because doubts have been raised in the international arena with respect to the safety of these compounds. Anticipated adverse effects were thyroid toxicity, genetic toxicity, cancer promotion, and developmental and reproductive toxicity. Therefore a closer look at the health effects of isoflavones is eminent.
Usually this kind of studies use information from studies with experimental animals. In this project a combination will be made of this (animal) information and epidemiological data from humans. This approach may overcome the necessity for extrapolating the animal data. This project will contribute to an improvement of current approaches in risk benefit assessment.

2.4.2 Aim of the project

The overall objective of this project is:
- to develop and strengthen integrated risk assessment/risk benefit assessment
- to investigate the use of similar biomarkers of exposure (e.g. serum concentration)
- to identify relevant methodological steps for an integrate risk/benefit assessment

Using information on the internal dose (exposure markers) and the comparison of gene expression profiles in both experimental animals and humans is a crucial step towards a direct comparison between animal (toxicological) and human (epidemiological) data, aiming at an integrated risk-benefit assessment of isoflavones.

As specific objective for the isoflavone case, the results of this project, in combination with those of the epidemiological ‘pillar’, may lead to an estimate of the level of isoflavone intake at which beneficial but no adverse health effects can be expected in humans.

2.4.3 Strategic and innovative aspects

This project will strengthen strategic collaboration between RUVM, WUR, TNO en RIKILT.

By performing this project two new items are involved:
1. the application of similar biomarkers of exposure (e.g. serum concentration) and of effects (e.g. gene expression) in both experimental animals and humans;
2. the use of transcriptomics to facilitate a direct extrapolation from effects observed in experimental animals to those that can be expected in humans.

2.4.4 Planned activities

The activities can be distinguished into several steps:
1. Bioavailability and internal dose. Using epidemiological data an inventory will be made of food items and supplements containing isoflavones.
2. Definition of relevant parameters for risk-benefit assessment. Mixtures of isoflavones will be tested in gene reporter assays using oestrogen receptor alpha (ERα) or -beta (ERβ) responsive cell lines, to study the estrogenic activity in comparison with the individual isoflavones (genistein, daidzein, glycitein). For this purpose different cell lines containing varying ratios of endogenous or transfected ERα and ERβ will be used.
3. Comparison of animal and human endpoints. In this step transcriptomic analyses will be used to link the toxicological and epidemiological data and to provide a direct comparison between effects in animals and humans.
4. Integrated ‘tox-epi’ risk-benefit assessment. The final phase of this project proposal will be the integrated risk-benefit assessment of isoflavones.
2.4.5 Planned products
For this project the following products are foreseen:
- paper(s) in peer reviewed scientific journals on in vitro effects of isoflavones in gene reporter assays (2011/2012)
- paper in peer reviewed scientific journal on in vivo gene reporter response (2012)
- paper in peer reviewed scientific journal on gene expression profiles (2013 or 2014)
- Ph.D thesis (2014)

2.4.6 Foreseen follow-up
By getting more insight in the practical application of integrating toxicological and epidemiological data into risk assessment knowledge and experience in this area at the Centre for Substances and integrated risk assessment (SIR) will increase. In addition, collaboration with the department of Toxicology and the department of Human Nutrition of Wageningen University in the framework of this project will also provide opportunities for future collaborations.

2.5 S/340001 Adverse effects of circadian disruption, Dr. A. de Vries

2.5.1 Motivation
An assumption exists that (night) shift work and breast cancer are related. However there is no evidence for a mechanism that could explain the observed associations. In this project the relation between breast cancer and shift work will be investigated. The obtained results will also increase an understanding of associations of shift work with other chronic diseases.

2.5.2 Aim of the project
The general aim of this project is to investigate whether working in night shifts leads to chronic health effects via a disturbance of the physiological circadian rhythm. The relation between shift work schedules and breast cancer development in mice will be investigated.
Specific objectives:
- objective 1A: Assess the causal relation between disruption of the circadian rhythm versus the incidence and malignancy of breast cancer in a well-controlled animal model. 1B: Investigate in the same animal model which changes in hormonal- and gene expression levels occur as a result of day/night rhythm disruption.
- objective 2: Investigate in a well-controlled animal model whether the observed changes in hormone- and gene expression levels after day/night rhythm disruption as identified in objective 1B depend on the type of shift schedule applied, mimicking night shift regimens frequently applied in The Netherlands.
- objective 3: Investigate in a well-controlled animal model the underlying mechanisms of circadian disruption in more depth, to find novel biomarkers which ultimately improve the validity of the biological index as prognostic tool of circadian disruption in humans.
2.5.3 Strategic and innovative aspects

Benefits of the studies in this project could ultimately be the mechanism-based development/design of better, healthier schedules in day/night working regimens for shift workers.

The proposed approach to analyze adverse effects related to working in night shifts is unique because

- the use of an innovative, physiological relevant, mouse model mimicking spontaneous human breast cancer development;
- it addresses the effect of different shift schedules.

2.5.4 Planned activities

According to the three objectives, several activities can be mentioned:

- analyzing the effect of a physically disturbed circadian rhythm in a unique mouse model mimicking human breast cancer;
- analyzing hormones to identify underlying mechanisms for the presumed relation between disruption of the circadian rhythm and breast cancer;
- developing the methodology and analyzing expression levels of several clock genes in circulating lymphocytes isolated from the circadian disrupted and control mice at different ages;
- testing the effect of several rotation schedules;
- Identifying new serum biomarkers for using sera from the animal studies to identify new biomarkers associated with circadian disruption and increased breast cancer risk; genomics analysis of molecular events preceding breast cancer development in circadian disrupted animals.

2.5.5 Planned products

Several products are envisaged to be carried out:

- networks with researchers involved in night shift work studies, circadian disruption and breast cancer;
- peer reviewed publications;
- PhD thesis;
- an assessment report on the public health risks associated with disturbed circadian rhythm i.e. the attributive risk will be assessed.
- a symposium to be held at the RIVM to introduce knowledge on the potential health effects of shift work to the broader RIVM researcher public.

2.5.6 Foreseen follow-up

In a follow-up the implications of the results of this SOR-project will be discussed with the Ministries of Health (VWS), VROM (for environmental stress related issues) and Social Affairs (SoZaWe) for shift-work related issues. In a later stage these investigations may serve as a science-based advice for policy measures to limit the incidence of circadian rhythm disruption-related chronic diseases due to the implementation of optimized night shift schedules.

Advice (to SZW) on better-designed, evidence-based nightshift protocols, leading to less severe adverse effects.
2.6 S/340030 Nanotechnology, Potential Risks Dr. W.H. de Jong

2.6.1 Motivation

Nanotechnology (NT) is the design, characterization, production and application of structures, devices and systems by controlling the shape and size at the nanometer scale. New nano-sized materials may be used in cosmetics, pharmaceuticals, medical technology products, household products like paint and food technology. The small size is accompanied by special characteristics such as increased chemical and physical (re)activity. This main specific characteristic also allows the potential interaction of nanoparticles (NP) at subcellular level.

Recently there has been an increase in the awareness that the production and use of NT products may be accompanied by both environmental and health risks. Although current methodologies are useful for evaluating certain risks of NT products, it is expected that not all potential risks of NT will be covered. So, new methods need to be developed. An integrated approach is needed for hazard identification and risk evaluation for man and environment, including chemistry, cell biology, (eco)toxicology, pathology, (toxico)kinetics, and modelling.

2.6.2 Aim of the project

The overall aim is to improve our understanding of fate, biological activity and associated environmental and health risks of NP, to contribute to (inter)national policy development. The aim of the project is to systematically investigate how physical and chemical properties of NPs (such as size, shape, surface area, chemical composition, and surface coating) influence their biological behaviour including their toxicity. Specific aims:

- To obtain insight into the environmental fate and effects on environmental species to assess the ecological risk of the release of NP into the environment.
- To investigate the toxicity of NP in vitro and in vivo, and to investigate mechanisms of toxic effects and how particle characteristics determine the toxicity of NP.

2.6.3 Strategic and innovative aspects

Worldwide there is a great need to properly assess the human health and environmental risks of NPs. In view of the RIVM strategy to play a leading role in risk assessment in Europe, it is crucial that activities are initiated that allow risk assessors at RIVM to maintain its position, and initiate new activities for a class of substances possessing fundamentally differing properties compared to the substances assessed up to now. The project will gain knowledge on both environmental and biological (health) effects of NP, and insight in the mechanisms/characteristics by which the behaviour of NP is governed in terms...
of potential adverse effects. One of the innovative aspects of the project will be the approach of the project in which risk assessors, (eco)toxicologists, pharmacokineticists, experts on physical chemical properties of NP and mathematical modelers will be involved in creating the most relevant and efficient study design.

In view of the growing development and application of man-made engineered NPs, in the next decades many questions about the hazards and risks of NPs need to be answered. RIVM wants to be one of the Institutes providing answers to both policy makers and the public on safe use of Nanotechnology.

2.6.4 Planned activities

1. Environmental effects of nanotechnology
   - Evaluation of NP behaviour in environmental partitions.
   - Determination of effects on lower environmental species.
   - Selection of NP for evaluation in fish.
   - Determination of effects on higher environmental species including fish larvae and fish.

2. Health effects of nanotechnology
   - Evaluation of possible toxic effects of NP in in vitro systems.
   - Determination of possible mechanisms involved in effects on cells and cell function.
   - Selection of NP for evaluation in in vivo toxicity studies.
   - Determination of effects after in vivo exposure by inhalation, and oral exposure.
   - Evaluation of behaviour of NP by means of kinetic model.

2.6.5 Planned products

- Peer reviewed publications
- 2 PhD theses

2.6.6 Foreseen follow-up

The project will provide insight into potential hazards and risks of non degradable nanoparticles. This will provide RIVM risk assessors with knowledge how to interpret toxicity studies of nanotechnology products and nanoparticles. RIVM will benefit as it will be recognised as expertise centre for safety aspects of nanotechnology. In addition, sponsors of RIVM research may use the results to formulate more specific questions in relation to specific consumer products for future RIVM research.

Potential sponsors will benefit as basic mechanisms on nanotechnology safety aspects and nanoparticle behaviour will be explored in this project which will support sponsors to formulate more specific product related questions dealing with potential risks of nanotechnology products.

The whole of the EU will benefit as adjusted risk assessment methodologies are urgently needed to allow for a proper risk assessment. It has even been suggested to use the precautionary principle and ban all applications of nanoparticles until all is known on risks of engineered NP and sound safety evaluations have been made available.
The theme of Safety has rapidly gained (inter)national attention and RIVM has to develop new expertise in this field. Emergency Response Functions and Safety are important subjects within two RIVM research sectors. Several threats (chemical, biological and radiation) and accidents require a sensible preparedness and adequate response. From a biological point of view biological safety and outbreak management demand attention. From an environmental view, modelling of environmental quality (chemicals, radiation, and terrorism) and toxicological effects in humans are topics of particular interest.

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3.1 S/620001 QRA Instrument for Safety Policy, Dr. P.A.M. Uijt de Haag

Motivation

In the Netherlands Quantitative Risk Analysis (QRA) is solidly based in the external safety policy, in order to enable decisions on spatial planning. The method thus should be robust and transparent. This is a complicated issue, because each situation has its own specific details and circumstances and values for some safety parameters are hard to determine. It is important that risk reducing measures are valued correctly in the QRA. This project aims to consolidate the use of QRA by developing a robust method to value Safety Management Systems (SMS) and risk reducing measures and by studying the validity of QRA results in specific situations for the emergency response planning.

3.1.1 Aim of the project

The aim of the project is to improve the QRA method used for spatial planning and emergency response planning and to increase its credibility as a robust and transparent method, resulting in a firm basis for a complete QRA method. The focus of the project will be to incorporate SMS characteristics and risk reducing measures in a robust way into a QRA. Other objectives are, to improve the knowledge on the effect of site specific characteristics on hazard zones and to develop a method to address site specific characteristics into emergency response planning.

3.1.2 Strategic and innovative aspects

The project addresses a number of strategic and innovative goals. The project will consolidate the position of RIVM as knowledge institute and front runner in the area of safety and emergency response, both in the Netherlands as well as in Europe. The project will be innovative by merging two different research fields, namely the study of characteristics of a SMS and risk reducing measures on one hand and the QRA method for spatial planning and emergency response on the other hand. The project will improve the possibilities of international collaboration and access to international projects by positioning RIVM as a research institute.

3.1.3 Planned activities

1. Selection of pilot installation.
   A set of criteria will be defined to select a pilot installation e.g. the storage of LPG or the unloading of chemicals.
2. Survey of the important aspects of the Safety Management System for the pilot system.
   An overview will be made of all aspects of a SMS that are important to the prevention of major hazards.
3. Survey of important preventive technical risk reducing measures for the pilot system.

4 The project is linked to a number of other projects, like projects of Dutch and EU working groups and other SOR-projects (CFD modeling of the environment and Evaluation of safety measures, both 2005-2006).
An overview will be made of possible preventive risk reducing measures.

4. Survey of the availability of methods to quantify aspects of the Safety Management System and preventive risk reducing measures in a QRA.
   An overview will be made of existing methods to quantify the important aspects of the Safety Management System and the effect of preventive risk reducing measures, including methods like Safety Integrity Level classification and Layer Of Protection Analysis. Also the application of fault tree and event tree modelling will be evaluated.

5. Development of a method to quantify aspects of the Safety Management System and preventive risk reducing measures in a QRA.
   A new model will be developed for the quantification of the Safety Management System and the effect of preventive risk reducing measures.

6. Survey of important mitigating risk reducing measures for the pilot installations.
   Based on a literature search and interviews of experts, an overview will be made of possible mitigating measures and their effectiveness.

7. Quantification of mitigating risk reducing measures for the pilot installation in a standard QRA. The effect of mitigating measures will be quantified. In case data are missing, a method will be discussed to overcome this problem, e.g. by setting up an expert judgment study.

8. Study on the influence of location-specific characteristics on the hazard zones and the effect of mitigating measures.
   For a limited number of practical situations, CFD modelling will be applied to evaluate the consequences of the location-specific characteristics on the hazard zones and on the effect of mitigating measures.

   Based on the CFD results, guidelines are drafted to describe the influence of location-specific characteristics on the hazard zones and their impact on mitigating measures.

10. Development of an integrated QRA method.
    The results of the quantification of preventive measures, SMS characteristics and mitigation measures will be integrated in a QRA method for spatial planning.

11. Application of the integrated QRA method to other installations/activities.
    The development of the integrated QRA method for the pilot installation will be tested on another type of installation.

3.1.4 Planned products

- Database with both standard procedures and measures for a number of selected installations and identified additional risk reducing measures.
- Presentations at symposia in the field of risk management, in particular the ESREL and Loss Prevention symposia.
- Peer reviewed publications in journals in the field of risk management, in particular the Journal of Hazardous Materials.
- An improved, robust QRA method for spatial planning near activities with dangerous substances.

3.1.5 Foreseen follow-up

The results of the project will be valuable to the Dutch government and, of course, to the society, since it will aid in implementing cost-effective measures.
The demonstration of the principles of this improved QRA method will follow-up in the elaboration into a complete QRA method that is accepted for spatial planning in the Netherlands.
3.2 S/660001 Research Cooperation in Human Toxicology, Dr. J. Meulenbelt

3.2.1 Motivation
The RIVM has an increasing responsibility to act as an emergency response organization in the field of infectious diseases, chemical and ionizing radiation incidents. Based on an audit, it was decided to strengthen both strategic and applied research in the emergency response function. Health-care workers and incidental relief personnel need this information to prevent unnecessary exposure and health risks for themselves before they enter the incident scene. They also need this information for adequate intervention measures to prevent further escalation. A number of strategic core fields of expertise lines are selected that are considered vital for the long-term. For these core fields NVIC (National Poisons Information Centre) strives after further deepening of knowledge and expertise.

In the field of Clinical and Forensic Toxicology, it is expected that in the future these disciplines are urgently needed in poisoning response function/emergency response function. This is reflected in a yearly increase in the number of advices provided by the NVIC on acute poisonings.

3.2.2 Aim of the project
The overall aim of this proposal is to strengthen, expand and formalize the cooperation between the Division MEV with the University Utrecht (IRAS), and also with the National Forensic Institute (NFI) in a multi-year research program. More specifically the objective is to reduce uncertainties in effect assessment in humans following exposure to toxic agents. This will be accomplished through research on differences in metabolism and target organ susceptibility leading to a better exposure-effect assessment in humans. Consequently, a better interpretation of analytical results will be possible.

3.2.3 Strategic and innovative aspects
In contrast to pharmaceuticals knowledge on human toxicological issues (with focus on inter-individual effect variability based on polymorphism in metabolism and individual target organ susceptibility for xenobiotics) is limited for chemicals. With this knowledge a more accurate acute human effect assessment after exposure to chemical substances is possible and better advice about poisonings can be provided. This knowledge will clearly improve the poisons response function. The achieved knowledge also enables the development of more precise effect assessments for exposure intervention guideline levels. Collaboration in research with the NFI will increase the possibilities to exchange knowledge on clinical en forensic toxicological issues between the institutes. A more formalised research cooperation with IRAS of the University Utrecht increases the possibility to spend research budget more accurately.

5 The project is related to SOR-project “Exposure testing after terrorist attacks”
3.2.4 Planned activities

1. PhD 1: Study on human variability in biotransformation with focus on enzymes involved in the metabolism of THC (and other cannabinoids) and some designer drugs. Performing primarily in vitro or if necessary in vivo animal or human studies on different enzymes related to the metabolism of cannabis and some designer drugs.

2. PhD 2: Study on human variability in target organ susceptibility (e.g. expression, function and regulation of receptors and receptor drug interaction) of cannabinoids and some designer drugs. Performing in vitro or if necessary in vivo animal studies on cannabis receptors to investigate differences in responsiveness because of polymorphism of cannabis receptors and some designer drugs.

3. Both PhD-studies: performing specific in vitro or in vivo animal or human studies
   - For better understanding of the mechanisms of induced effects of cannabis or some designer drugs based on results obtained in previous year; toxicokinetic and toxicodynamic healthy volunteer studies
   - For better understanding of the mechanisms of induced effects based on results obtained in previous years; toxicokinetic and toxicodynamic healthy volunteer studies
   - Developing Physiologically Based PharmacoKinetic-PharmacoDynamic models (PB-PKPD models) of the compounds under investigation.

3.2.5 Planned products

- Physiologically Based PharmacoKinetic-PharmacoDynamic models
- Publications in international peer reviewed journals
- Two (or more) PhD theses

3.2.6 Foreseen follow-up

This research will strengthen the position of the poisoning response function and consequently the emergency response function. Furthermore, the research network between RIVM, IRAS and NFI in the field of clinical and forensic toxicology, will strengthen other RIVM research programs such as on medicines and functional foods, and environmental quality and public health. It is anticipated that with the achieved knowledge the funding for new projects can be obtained.
The theme Infectious Diseases potentially covers all research questions, ranging from source of infection to effective intervention. Although most of the potential work will fit best in the sector of CIb (Centre for Infectious Disease Control), also food safety issues are relevant, especially on the level of sources of contamination. Immunology, vaccination and genetics are specific areas that need to be strengthened within RIVM. Besides this, effect studies and modelling issues are important.

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4.1 S/210026 Modelling the Future of MRSA in NL, Prof. Dr. H. Grundmann

4.1.1 Motivation
The global epidemic of methicillin-resistant Staphylococcus aureus (MRSA) is characterized by the spread of a number of epidemic strains worldwide. Most MRSA infections are acquired in health care settings, and MRSA has become a marker for the failure to contain antimicrobial-resistant pathogens in hospitals. The dynamic expansion of health care-associated MRSA (HA-MRSA) is characterized by four factors, i) hospital/nursing home transmission, ii) infrequent transmission among healthy individuals outside health care settings, iii) long duration of carriage, particularly among chronically ill patients, iv) frequent reintroduction into the hospitals. These four features explain why the MRSA epidemic is maintained by a “core” group of vulnerable, typically older, chronically ill members of the society and also account for the relatively slow increase of the MRSA prevalence (several years) as published in many longer time series studies and recorded by national and international surveillance initiatives.

An analysis of the health care utilisation patterns (HCUP), based on available data of patient movements between health care institutions in the Netherlands, will therefore be able to anticipate the future scale of the problem. In this way, control strategies (such as admission screening and the search and destroy approach) can also be put into an evolving epidemiological context and their long-term cost-effectiveness be appraised.

4.1.2 Aim of the project
Strategic decisions on the control of MRSA would greatly benefit from an understanding of patient movements between hospitals, long-term care facilities, nursing homes and the community. It is the aim of the project to develop a solid and quantitative analysis of the spatiotemporal dispersal of MRSA using defined mathematical models based on the observed HCUP in The Netherlands. The following specific objectives will be achieved:

- To scale the spatiotemporal movements of patients
- To reconcile patient movements with MRSA prevalence data
- To develop a multi-institutional meta-population model
- To develop a spatiotemporal model for MRSA dispersal
- To determine the cost effectiveness of various intervention strategies
- To implement a country-wide monitoring tool for MRSA

4.1.3 Strategic and innovative aspects
Quantitative ecological models are recently emerging as decision support tools for the control of health care-associated infections. Key to their predictive validity is the availability of accurate empirical data. In The Netherlands - in contrast to many other countries - these data are available. This poses a unique opportunity for the development of a 'quantum leap' research agenda into the dynamics of MRSA, the most important nosocomial and antimicrobial-resistant

6 This project is related to the projects "The impact of healthy ageing on health care use and costs", "Transmission models in health care", "Health economics of interventions in AMR".
pathogen at a time when The Netherlands would most decisively benefit from sound advice for future policy decisions.

4.1.4 Planned activities

1. Scaling the spatiotemporal movements of patients in, out, and between health care institutions. This requires data on hospital admissions for the Dutch population, which are available at Centraal Bureau voor Statistiek (CBS).

2. Reconciliation of patient movements with MRSA prevalence data and stochastic transmission models (parameter setting) This is based on the scaling of the movements between different compartments of the health system as described above.

3. Development of a multi-institutional meta-population model. This involves the development of a model representation of “the average” Dutch health care collective, consisting of any number of health care institutions and the catchment population served by a single tertiary care hospital.

4. The development of a spatiotemporal model for MRSA dispersal in the Netherlands shall take into account the experiences of all models generated above and generate a multi stage meta-population model by concatenating the observed multi-institutional health care collectives into the virtual reality of the Dutch Health Care Network.

5. The determination of the cost effectiveness of various intervention strategies through sensitivity analyses is already inherent to many of the previously described activities.

6. The implementation of a country-wide monitoring tool for the spatiotemporal occurrence of MRSA will take advantage of the experience accumulated during fulfilment of objective 1 and 4.

4.1.5 Planned products

Fulfilling the above mentioned tasks will render at least one publication for each of the six objectives and activities in a peer reviewed journal as given below:

- Scaling patient movements
- Reconciling model
- Meta-population model
- Spatiotemporal model
- Economic evaluation
- Monitoring dissemination

4.1.6 Foreseen follow-up

On the Dutch national level various stakeholders will profit from this project:

- The models developed by the project will provide insight for Health policy and finance decision makers in the light of the changing epidemiology and containment costs in The Netherlands.
- Regional, local health administrators will benefit from a quantitative assessment of the effects of insufficient control efforts by individual health care institutions.
- Executives of health care institutions and Infection control teams can use the developed tools to determine the cost effectiveness of various interventions.
- Finally, the scientific community will choose to validate and further expand on the national models to increase the understanding of the population dynamics and evolution of antimicrobial resistance.
4.2  S/210066 Who infected whom, Dr. J. Wallinga

4.2.1  Motivation
Key questions in infectious disease epidemiology are: "how effective are implemented control measures in reducing transmission of infection?" and "how effective should control measures be to control an epidemic?" Both questions can be answered if we have information on two key variables that describe spread of infection: the generation interval and the effective reproduction number R. We can estimate these two key variables if we know exactly who infected whom. The real problem in answering questions in infectious disease epidemiology, therefore, comes down to answering the question "who infected whom?"

Infectious disease epidemiologists collect data on the epidemiological characteristics of infected cases, such as their age, gender, time of symptom onset. This provides a valuable source of information that allows us to make epidemic curves. Microbiologists and virologists, on the other hand, are characterizing the fingerprint of pathogens using molecular techniques, for example using the sequence of nucleotide pairs of viral RNA. This provides a valuable source of information that allows us to make phylogenetic trees. The ‘traditional’ epidemiological data allows for inference of the effective reproduction number R and the generation interval . Also the ‘molecular’ sequence data allows for such inference. As methods for molecular sequencing become faster and cheaper, it is increasingly common to have both reliable ‘epidemiological’ data and reliable ‘molecular’ sequence data. The foot-and-mouth outbreak in the UK in 2001 and the SARS epidemic in Singapore in are perhaps the best known examples of infectious disease outbreaks with both ‘traditional epidemic’ and ‘molecular sequence’ data. For both the SARS and foot-and-mouth outbreaks the estimated transmission paths resulting from molecular sequence data did not always match up with those of traditional epidemiologic data. This begs the question how we can combine both sources of information to come up with a single and improved integrated analysis of transmission paths and parameters to underpin our recommendations for infectious disease control.

There exists a range of methods that bridge the gap between analysis tools for ‘molecular’ sequence data (phylogenetic trees) and analysis tools for ‘traditional’ epidemic data (epidemic curves). The availability of this range of methods would allow us to tailor analysis tools to the data at hand. Rather than throwing data away because it cannot be used in the analysis, we can use all the epidemiological and molecular sequence data we have to reconstruct who-infected-whom in a single analysis, estimate the key epidemiological parameters, assess effectiveness of control measures, and use this to underpin decisions for infectious disease prevention and control.

4.2.2  Aim of the project
Our extremely ambitious aim is to integrate traditional epidemic data and molecular sequence data, and reconstruct transmission paths and ancestral lines of the observed pathogen sequences, as well as key epidemic parameters such
as the reproduction number and generation interval that are necessary to assess the effectiveness of interventions. That is, given the observed case reports and molecular sequence data, we aim to answer the question “who infected whom?”

4.2.3 Strategic and innovative aspects
This project bridges a gap between analysis tools for molecular sequence data and analysis tools for traditional epidemiological data. A separate analysis is likely to result in two contradictory conclusions from two different sources of information. We must have methods that use one single analysis of all available data to underpin decisions about infection control.

4.2.4 Planned activities
We will rephrase coalescent theory in the terminology that is used for describing infectious disease transmission models.
Overview of available data: this is key to measuring whether the new methodological lead to advancement of our understanding of infection transmission, and to improved precision of our estimates of epidemic parameters, and to correct assessment of the effectiveness of interventions. Next we will derive a joint distribution for generation interval and number of nucleotide substitutions between two pathogen sequences that are sampled from a secondary case and its primary case.
(a) To further extend earlier work we will first adapt existing methods to analyze epidemiologic data to allow for missing or misclassified links between cases. (b) Reconstructing links to unobserved (asymptomatic, unreported) cases in incompletely reported disease surveillance: Tuberculosis as an example. (c) By reconstructing links to observed cases (4a) and links to unobserved cases (4b) we have all ingredients to build a transmission tree. Inferring key epidemiological parameters, including effectiveness of interventions, from reconstructed transmission trees.

4.2.5 Planned products
Publications in international peer-reviewed scientific journals:
Coalescent theory for infectious disease epidemiologists: a tutorial.
Frequency of observed differences between pairs of infector and infectee: towards a joint likelihood function of the generation interval and the genetic distance.
Reconstructing missing links in completely reported infectious disease outbreaks: pneumonic plague as an example.
Reconstructing properties of asymptomatic, unreported and missing cases in incompletely reported disease surveillance: hepatitis B as an example.
Reconstructing transmission trees using likelihood-based methods and pair-based likelihood functions.
Inferring key epidemiological parameters, including effectiveness of interventions, from reconstructed transmission trees.
A PhD thesis.

7 Related projects: This project builds heavily on the expertise accumulated in the ongoing project, S/210046 “Epidemic Modeling of Molecular Data”.
4.2.6 *Foreseen follow-up*

Direct applications of the tools developed in the proposed project could include the following:
- Making a scientifically sound statement of the probability that one case has infected another when such statements are required in court;
- Providing clear directions for which type of contacts to include and exclude in epidemiological contact tracing for control of tuberculosis;
  - Assessing the impact of an intervention during an outbreak, using all collected epidemiological and molecular sequence data, even when a vast majority of cases is asymptomatic, even if few cases are sampled to obtain the molecular sequence of the pathogen, and even if the various pathogen strains have evolved different epidemic characteristics.

4.3 *S/210076 Timeliness respons outbreaks, Dr. M.E.E. Kretzschmar*

4.3.1 *Motivation*

In view of the threat of a future pandemic outbreak of any highly pathogenic pathogen strain, including influenza, with possibly devastating numbers of deaths, health authorities all over the world are designing plans to prepare adequate responses to such an outbreak. Possible intervention strategies for pandemic influenza range from treatment with antiviral drugs, contact tracing and isolation, increasing social distances by closing schools and other public meeting places, to vaccination. The use of mathematical and simulation models has become an accepted means to test and evaluate the effectiveness of different interventions.

The effectiveness of a response in containing an outbreak is largely determined by three quantities, firstly the completeness, secondly the timeliness and speed of every link in the response chain, and thirdly the effectiveness and coverage of reaching individuals who are targeted by intervention. Completeness is determined largely by the awareness of reporting GP’s. Timeliness and choice of interventions are determined by the clinical course of infection and its transmission dynamics and by the diagnostic tools available to (rapidly) identify infected individuals. The problem of underreporting of infectious diseases may serve as an example for the interaction of infection, response chain and control measures.

Another point of attention is the behavior of populations. Understanding and making use of the influence of social networks and the underlying mechanisms of decision in conflicts between individual and population interests will greatly enhance the ability of rapid response mechanism to adequately roll out public health interventions.

4.3.2 *Aim of the project*

The aim of this project is to develop a theoretical framework in which to (a) classify (newly emerging) pathogens according to properties that determine in which way they challenge the public health response; (b) identify the steps of the response chain that constitute an adequate response to any outbreak; (c) identify the extent of underreporting for notifiable diseases; (d) develop a mathematical model that can simulate and analyse the interaction between
pathogens and a generic outbreak intervention; (e) use the model to identify the crucial and possibly weak links in the response chain, quantify their expected duration based on empirical data, and quantify the effectiveness of interventions; (f) investigate how the properties of the interaction between outbreak of a pathogen and public health response might change in times of crisis; (g) formulate recommendations for a flexible and regionally oriented intervention strategy; (h) evaluate how changes in reporting responsibilities as defined by the new law on Public Health might affect timeliness and reporting; (i) identify region specific key components for improvement of the reporting to respond chain.

4.3.3 Strategic and innovative aspects

The first innovative aspect is the idea to dissect the transmission and response process into smaller interacting units and to look at the relationship between infectious agent and response in a generic way by viewing them as one interacting system. The idea to investigate the relationship between social network aspects of human behaviour and the implications for the effectiveness of outbreak response implies a combination of methods from social sciences and mathematics/statistics to come to new insights for public health policy. Investigating relationships on the regional level will give new insights into the relationship between the demographic and ethnic characteristics of a population and the effectiveness of outbreak response. Finally, we plan to use concepts from game theory and game theoretical aspects of social network interactions, to develop a flexible way of thinking about response planning.

4.3.4 Planned activities

1. Classification based on literature review of known (emerging) infections according to their clinical and transmission features determining how an outbreak progresses and where response measures can intervene.
2. Identification of relevant response measures and description of the response chain.
3. Identification of crucial factors to quantify the reporting delay. Similarly, identification and measurement of factors determining patient delays.
4. Collection of empirical data concerning (a) clinical and transmission features identified in 1 for some selected (emerging) infectious diseases and (b) quantification of duration and effectiveness of steps in the response chain as identified in 2 and 3.
5. Collecting empirical data concerning regional differences in the response chain for (emerging) infectious diseases through the GGDs in the Netherlands
6. Description of steps in the response chain that are influenced by social networks of target population
7. Development of mathematical framework to describe interaction of outbreak and response chain
8. Calculation of size and extent of underreporting for a set of specific diseases, and modelling the effect of underreporting in timeliness of outbreak detection
9. Incorporation of social network effects into model

* Related projects: the project is related to the ongoing SOR project Tracking emerging epidemics.
10. Investigation of game theoretical approach to effectiveness of intervention measures
11. Identification of weak links in the response chain, most effective intervention strategies depending on type of (emerging) infectious diseases, data needs for better evidence base of intervention
12. Formulating recommendations for improving effectiveness of the response chain and for formulating public health messages (social network and behavioural effects).

4.3.5 Planned products
The main product of the project will be a PhD Thesis consisting of at least 5 papers published or publishable in international journals and two papers on size and effect of underreporting. The papers for the PhD thesis could focus on: (a) a classification of infectious diseases in terms of time scales of relevant dynamic processes and interventions; (b) model definition and analysis of some example diseases; (c) case studies for specific infectious diseases based on notification data (e.g. new influenza A|H1N1 notifications); (d) analysis of the possible impact of contact tracing for specific infectious diseases (e) regional differences in the effectiveness of response. Further products:

- A mathematical model, to collect the relevant data for parametrizing the model and to properly interpret the modelling results,
- A tool for improving completeness and timelines of the reporting and response chain.
- Recommendations for regional improvements in the reporting and response chain.
- Measurements of the effect of implementation of the improvements in the reporting and response chain in different GGD regions.

4.3.6 Foreseen follow-up
The results will contribute to identify those links in the response chain that are most amenable for improvement in practice. Furthermore, it aims at a generalization of the contingency planning as is now conducted for pandemic influenza and can potentially help preparing the public health system for outbreaks of yet unknown pathogens. Finally, the results will be used to formulate region specific recommendations for improving the performance of the local response to infectious disease outbreaks.

4.4 S/230136 Whole Genome Analysis of M. tuberculosis, Dr. D. van Soolingen

4.4.1 Motivation
In the last decade several DNA fingerprinting methods have been used to study transmission of tuberculosis (TB), as well as the phylogeny of the causative agent; Mycobacterium tuberculosis. One of the apparently most clonal groupings of M. tuberculosis is the Beijing genotype family. Recently, a worldwide survey revealed that Beijing strains are emerging often associated with drug resistance, more virulent in animal models and associated with relapse of tuberculosis. Currently, the most important question is how recently the Beijing genotype strains started spreading and how clonal strains of this genotype family are. Furthermore, the differences between the emerging modern Beijing lineage and the ancestral Beijing lineage need to be investigated. To answer these
questions, Beijing genotype strains of the ancestral and the modern lineage should be compared by whole-genome sequencing.

4.4.2 **Aim of the project**

There are two specific aims related to this project:

- To determine the genetic changes in the whole genome of *M. tuberculosis*, passed on from person to person.
- To determine the genetic relatedness (clonality) of typical Beijing genotype isolates from a wide spread area by investigating the rate of mutual variation.

4.4.3 **Strategic and innovative aspects**

Previously, whole genome sequencing was laborious and expensive and the international literature is restricted to whole genome sequencing studies of a few highly diverse strains. Also, the clonality of the most successful *M. tuberculosis* genotype families (Beijing and Haarlem) in the worldwide TB epidemic has not been determined. Whole genome sequencing is the most complete and accurate approach for this research purpose. Both the method and the research questions to be addressed are new and innovative. It is expected that whole genome sequencing of micro-organisms in general will be the method of the future. This research will reinforce the international position of the RIVM. If the findings in this project are in agreement with the expectations, whole genome sequencing will increasingly be explored in the research and diagnosis of infectious diseases the future.

4.4.4 **Planned activities**

In total, 15 *M. tuberculosis* strains will be subjected to whole genome sequencing. The duration of the project will be three years. In the first six months the strains will be selected and cultured for DNA isolation. In the next year the 15 strains will be subjected to whole-genome sequencing by a commercial party and confirmation of mutations. The last 18 months will be used for confirmation of mutations, analysis of the data, and publication of the results.

4.4.5 **Planned products**

1. Revelation of the entire genome sequences of 15 *M. tuberculosis* isolates of various lineages. This will add significantly to the scientific community, where currently only two *M. tuberculosis* genomes are available.
2. Insight into the evolutionary development of the genome of *M. tuberculosis* under the pressure of human-to-human passage in a 15-year period.
3. The possibility to use genetic changes anywhere in the genome of *M. tuberculosis* to trace exact transmission routes of (genetically slowly changing) *M. tuberculosis* strains in the community. Ideally, the primary-, secondary-, and tertiary- sources of infection in TB

9 This research project fits in the regular surveillance project on transmission of tuberculosis in the Netherlands.
epidemics can be distinguished in this way. This will provide the possibility to analyze more accurately how transmission chains build up and no longer consider long-term clusters of TB cases in the molecular epidemiology as one cluster, but as separate time-marked transmission chains.

4. A comparison of the clonality of six Beijing genotype isolates from wide-spread areas. On the basis of the observed rate of DNA polymorphism in the six Beijing genotype strains, conclusions can be drawn on how recently the Beijing genotype strains started their worldwide spread. This is highly important in the context of the recurrent tuberculosis epidemic.

5. A comparison of three ‘ancestral’ and three ‘modern’ (emerging) Beijing isolates and thereby insight in the changes in the genome of Beijing strains that may have contributed to their successful worldwide dissemination. This comparison may supply information on the differences in virulence and ability of BCG-vaccine escape between these two groups of strains.

4.4.6 Forseen follow-up

The whole genome analysis will, after interpretation and publication of the results, be made available to all international researchers working in the field. As only few whole genome sequences are available at the moment this will internationally be highly appreciated.

The investigation on the clonality of the Beijing genotype isolates will facilitate new research in the field of the phylogeny of M. tuberculosis. Furthermore, the comparison of ‘ancestral’ and ‘modern’ Beijing strains may initiate new research on the pathogenesis of Beijing strains.

The analysis of the genomic changes in M. tuberculosis strains in long term transmission chains will provide the basis for research on the development of new genetic markers with a fast- and a slow pace of the molecular clock.

The experiences with whole genome sequencing may facilitate the next step of this tool in the microbiology; the use of this technique for identification, genetic fingerprinting and prediction of resistance to antibiotics.

4.5 S/230156 Transmission intervention stratagies, Dr. ir. E. Duizer

4.5.1 Motivation

Food borne illness has been documented for several groups of pathogens that infect persons after oral ingestion. Viruses, and foremost noroviruses (NoV), are currently recognised as major food borne pathogens in industrialized countries. Contamination control often relies on methods detecting the presence of indicator organisms such as bacteriophages or E. coli. However, data obtained with these methods do not correlate with the presence of viruses. Moreover, molecular based tools to detect the presence of viral RNA (or DNA), does not necessary indicate infectious viruses. State of the art approaches are needed to obtain inactivation profiles for noroviruses (and other food borne viruses) to be able to determine viral infectivity reducing methods in the food production
process and areas. Ultimately, this will allow us to draft protocols that will reduce the number of infections due to either food borne or environmental transmission.

4.5.2 Aim of the project
The aim of this project is to reduce the burden of (food borne) fecal-oral viral infections by presenting science based protocols for transmission intervention and to provide a tool for the assessment of the likelihood of food borne transmission of (emerging) viruses.

4.5.3 Strategic and innovative aspects
The innovative aspect of this project is that human NoV strains will be used to determine the infectivity in stead of model viruses. The detection method is based on a novel low-shear-stress rotating cell culture system for three dimensional tissue-like aggregates. An up to date tool-database system for the assessment of likelihood of food borne transmission of emerging viruses is relevant to enable implementation of effective intervention strategies. This approach is new and timely and the result will allow us to maintain our leading role in the world in the field of viruses and food safety.

4.5.4 Planned activities
The project can be divided in two research lines (1 and 2) of which each has several objectives:

1. Development of tools for the assessment of food borne transmission of viruses.
   - Implement the NoV infectivity assay.
   - Perform laboratory experiments to assess temperature, chlorine and pH dependent inactivation, the effectivity of commercial available disinfectants and the sensitivity for freezing/thawing cycles, drying and UV radiation of several enteric viruses.
   - Perform laboratory experiments to fill the gaps in data needed for the database on likelihood of food borne transmission.
   - Draft criteria for the extrapolation of inactivation data obtained by molecular detection methods to rates of reduction in infection.
   - Develop criteria and features that determine the success of viruses for food borne transmission.
   - Produce a tool to assess the likelihood of food borne transmission.

2. Production of protocols for intervention of the transmission of food borne viruses.
   - Analyse food production chains
   - Implement detection methods for viruses on food
   - Assess viral load reduction in post-contamination treatments of foods.

10 Related projects: V/230461/01/EV Transmission and control of enteric viruses, V/300100/07/AA Voedsel gerelateerde virusinfecties, ENVIRONET, V/330140/07/VO Virussen in Voedsel
• Test measures to prevent food contamination.
• Draft protocols to increase bacterial and viral food safety.

4.5.5 Planned products
• Techniques and methods, standard operating procedures for the detection and inactivation of noroviruses and protocols for the prevention of contamination
• A database containing structural virological information and inactivation profiles
• Vital knowledge on effective disinfection methods for the enteric viruses will be generated as well as a tool (database) to support in assessment of likelihood of food borne transmission of emerging viruses.
• Development of networks. The interchange of expertise’s and strengthening the collaboration between RIVM and other research groups is a major asset of this project.
• Fact-sheets with the data obtained on the inactivation profiles.
• Progress reports for the graduate school VLAG and the SOR programme.
• Five peer reviewed publications
• PhD thesis

4.5.6 Foreseen follow-up
This project will contribute directly and indirectly to the production of science based protocols for the intervention of transmission of enteric viruses. As such the CIb (foremost LCI), the public health services (GGD) and food handlers and food industry will benefit from the results. Since part of the project will aim at developing, evaluating and implementing assays to study the effectiveness of intervention/inactivation methods for viruses, we will be better equipped in the future to produce data needed for risk assessment of emerging viruses. Additionally, the database that will be constructed for the assessment of likelihood of food borne transmission of viruses will be maintained and put to use if viruses do emerge.

4.6 S/230166 Zoonotic helminth infections and allergy, Dr. B. E. Pinelli Ortiz

4.6.1 Motivation
In the Netherlands, different animal species are infected with helminths such as Trichinella, Toxocara, Echinococcus, and Ascaris that can also infect humans. A study carried out at the RIVM showed that the Toxocara seroprevalence is 19% on average, with 4 % to 15% in people younger than 30 years up to 30 % in people older than 45. A recent serological survey revealed that pigs are often infected with A. suum. Dutch citizens could be exposed since eggs of A. suum have been found in sewage sludge that is widely used as fertilizer.

Evidence from various studies suggests that helminths modulate the host immune response and affect other immunopathologies such as allergies. To get a better understanding of the mechanisms involved in the negative or positive correlation between allergic asthma and helminth infection, early immune responses have to be investigated in detail.
4.6.2 **Aim of the project**

The aim of the present project is to identify helminth antigens and their role in immunoregulation (studies carried out within Cib-6) and to use the identified antigens in order to:

- Improve and/or develop new assays for the serodiagnosis of endemic helminth infections.
- To evaluate the effect of different helminth antigens on experimental allergic asthma. This study will allow us to test the working hypothesis: The effect of helminth infection on allergy depends on the helminth species involved. Therefore, antigens derived from different helminth species will affect allergic manifestations differently.

4.6.3 **Strategic and innovative aspects**

In The Netherlands serodiagnosis of infections with Toxocara spp., Ascaris spp. and Trichinella spp. is only carried out at the RIVM. The use of purified antigens derived from different helminths will be crucial in the attempt to improve the currently available assays. Serodiagnostic assays with higher specificity and sensitivity may have worldwide application.

Emerging evidence indicate that infection with helminth affect the outcome of allergic manifestations. Identifying parasite antigens capable of suppressing allergic manifestations will open possibilities to develop novel therapeutics to prevent allergic diseases.

4.6.4 **Planned activities**

**Effect of helminth antigens on APC maturation**

This research project will start by characterizing the effect of helminth antigens on APC maturation. Maturation of APC will be evaluated by measuring expression of cell surface molecules and induction of cytokines by flow cytometry and ELISAs/RT-PCR respectively.

**Evaluation of purified helminth antigens and synthesized neo-glycans on APC maturation and T cells stimulation.**

Different glycan molecules present in T. canis E/S antigen have already been identified in a previous study and have been synthesized. The effect of neo-glycans TSL-1 and gp45 on DC and macrophage maturation will be followed by measuring expression of cell surface molecules and cytokine induction as mentioned above.

**Evaluation of the effect of purified helminth antigen on experimental allergic asthma**

Mature DCs that have been exposed to the helminth antigens of interest (based on results from in vitro studies) will be transferred by intraperitoneal injections to naïve BALB/c mice. Mice will then be exposed to the OVA-sensitization/challenge treatment and experimental allergic asthma will be evaluated by histological examination of lung tissue, cytokines and antibody production.

![Related project: SOR project Cib6; Diagnosis of human parasitic infections (Cib/LIS/PAM); Surveillance of parasitic animal infections (Cib/LZO/Parasitology).](pagina_102.png)
Improvement of serodiagnosis of helminth infections
Several antigens will become available during the first years of this project which will be used to improve the serodiagnosis of helminth infections.

4.6.5 Planned products
Our study will lead to the following publications in peer reviewed journals in the field of immunology/parasitology/glycobiology:

- Effect of different Helminth antigens on APC maturation. To be submitted December 2008.
- Effect of helminth antigens and neo-glycans on APC maturation and T cell priming. To be submitted November 2009.
- Effect of helminth antigens on experimental allergic asthma. To be submitted December 2010.
- Improvement of serodiagnosis of helminth infections. To be submitted December 2011.

Other foreseen products are:

- Availability of purified helminth antigens that could be used in the development of diagnostics tools for helminth infections.
- The methodology for DC transfer could be used with other models and molecules of bacterial and viral origin with immunomodulatory potential.
- "Vital knowledge" at the RIVM and increased collaboration with universities in the Netherlands and abroad (UK, Italy, France).
- Building and extending a network in the field of parasitology and Immunology will facilitate knowledge exchange and the possibilities for future grants.
- PhD thesis.

4.6.6 Foreseen follow-up
Results from this project will contribute to the fields of:

- Immunology, by getting a better insight into the role of helminth antigens in immunomodulation. Studies on the identification and characterization of purified helminth antigens are limited. However, the availability of molecules that could suppress immunopathologies such as allergies could have therapeutic application.
- Parasitology. Results from these studies will contribute to our knowledge on the characterization of purified helminth antigens and on information regarding parasite-host interactions.
- Glycobiology. Studies carry out in this study will provide information on the function of the synthesized neo-glycans and their use in immunomodulation serodiagnosis.

The Cib/RIVM will also benefit from this project since the immunological studies carried out in this study fits within the efforts in stimulating and improving immunological research within the Cib/RIVM. This will materialize in the future in the form of publications in peer reviewed journals, additional grant applications, PhD thesis and in the field of diagnostics in SOPs describing new tools for the diagnosis of toxocariasis and trichinellosis both important for humans and veterinary parasitology.
4.7  S/230406 Host Response to RSV (Respiratory Syncytial Virus), Dr. C.M. Janssen

4.7.1  Motivation
Infectious diseases are caused by the complex interaction between pathogens and their hosts. The pathogenesis of infectious diseases depends both on pathogen components, like virulence factors, survival and invasion mechanisms, and on host components like immune responses, to eliminate invading pathogens and resolve the disease. Traditional human infectious disease studies have focused on investigating properties of pathogens while fewer advances have been made in understanding the molecular basis of the host responses. One of the reasons for this slower advancement is the complexity of the host genome and its responses to pathogens. Over the last decade the genome sequence of human and other hosts (e.g. mice) have been unravelled and technical developments such as large scale genetic profiling and transcription profiling using micro-arrays, have now opened up a whole range of possibilities to study the role of host factors in host-pathogen interaction. This will ultimately lead to improved strategies for controlling infectious diseases.

The proposed project will focus on the host-response to Respiratory Syncytial Virus (RSV), which is a major health problem in children. Unravelling factors that are responsible for susceptibility to infection and induction of long-term protective immunity may lead to novel preventative or therapeutic intervention strategies.

4.7.2  Aim of the project
The overall aim of this project is to increase our understanding of host-mechanisms in the infection process and of the role of host-genetic factors in this interaction. We specifically aim to identify host-factors that determine differences in the course of infection and differences in the induction of long-term, protective immunity RSV. To this end we will:

- Study genes and biological pathways that are important in determining individual differences in susceptibility to severe RSV infection and, determine their role in the infection process.
- Compare host responses to respiratory pathogens after ‘natural’ (primary) infection with responses after re-infection either after vaccination or after primary infection, using micro-array analysis. This will enable us to assess how, and to what extent, vaccine-induced protection differs from “natural immunity”.

4.7.3  Strategic and innovative aspects
The combination of micro-array analysis in murine models of infectious disease with and without vaccine-induced protection, together with genetic studies in well-defined human patient populations, is a powerful multidisciplinary approach to increase our understanding of host-pathogen interaction, host-factors that determine susceptibility to infection, and vaccine-induced protection. Insight into the role of host-factors in host-pathogen interaction in RSV infection is also

12The project is complementary to two other proposals, "Immune pathways in vaccination" (project leader, Rob van Binnendijk) and "Memory immunity" (project leader, Annemarie Buisman)
highly complementary to other ongoing studies into pathogen factors in this process, which are extensively studied by other groups at RIVM. This approach may ultimately lead to the identification of factors that can be targeted to obtain optimal disease-protection, either by vaccination or by therapeutic intervention.

4.7.4 Planned activities

1. Importance of identified host pathways in human disease
   Preliminary analysis of our previously performed genetic association study revealed that polymorphisms in two classes of genes are associated with severe RSV disease: genes involved in innate immunity and, genes involved in asthma and allergy. The importance of these specific genes and pathways in human disease will be studied.

2. Comparison of host-responses after ‘natural’ infection and infection after vaccination.
   Using transcription profiling, pathways will be identified that are triggered by primary infection and re-infection, but not by vaccination and challenge. This approach is taken to ensure that we are able to identify early responses which will eventually lead to pathogen clearance. To investigate if responses in the lung are also reflected by changes in gene-expression in blood we will also determine transcription profiles of whole blood. For this purpose, the following approaches will be used:
   - Analysis of differences between vaccine-induced immunity and "natural immunity"
   - Analysis of differences between vaccine-induced immunity and vaccine-enhanced disease

4.7.5 Planned products

- This project is expected to gain vital insight into factors that determine protective immunity to RSV infection and factors involved in determining disease susceptibility.
- The project is expected to result in peer reviewed publications and a PhD thesis
- The project will help further establish the national and international scientific position of the RIVM in the host-pathogen interaction research field.

4.7.6 Foreseen follow-up

The understanding gathered in this project may ultimately lead to the identification of host-factors that could be targeted for the induction of optimal protection against RSV either by improved vaccination strategies or by therapeutic intervention.

The results will contribute to the prevention and control of infectious diseases. The knowledge gained in the proposed project, may eventually lead to the identification of critical target molecules and pathways for diagnosis and intervention. To fulfill its advisory role, the RIVM CIB depends on such knowledge. The results of this project will also directly contribute to the monitoring role of the RIVM CIB with respect to the "Rijksvaccinatieprogramma".

4.8 S/230426 Memory Immunity, Dr. A.M. Buisman
4.8.1 Motivation

Ideally, vaccination should provide protection for life by the production of high antibody titers. Unfortunately, both vaccine-induced and naturally-acquired immunity wanes, allowing reinfection to occur. Waning immunity has been proposed to a major cause for the remarkable resurgence of pertussis, which has been observed during last decades in a number of countries including the Netherlands. This makes pertussis one of the major vaccine-preventable diseases today. Waning immunity is currently mostly studied by assessing (decreases in) antibody titers. However, this approach neglects the role of cellular immunity in protection against infectious diseases. A better understanding of the persistence of memory immunity induced by vaccines is likely to lead to a more rationale choice of vaccine formulations and schedules to provide more sustained long-term-protection in the population.

4.8.2 Aim of the project

This project aims to get insight into the character, magnitude and duration of the cellular memory immunity against several vaccine components in Dutch populations and will focus on Bordetella pertussis.

- The primary objective is to assess the effects of removal of LPS and bacterial DNA due to the switch from PWCV to PACV on the long term cellular immunity to *B. pertussis* and also to the other components of the DTP-IPV-Hib vaccine in children aged from 3 to 9 years.
- The secondary objective is to assess cellular memory immune responses to other vaccine-preventable diseases.

4.8.3 Strategic and innovative aspects

This study will be the first one to study memory B-cell responses in populations of Dutch children.

During this project more techniques to identify pathogen-specific memory B-cells in even smaller volumes of human blood will be developed. This will allow us to study memory B-cell and T-cell responses in populations of infants. This project will explore techniques which can be used to measure cellular immunity to several other pathogens as well. More knowledge about memory immune responses to vaccine-preventable diseases makes it possible to better substantiate the use of modern vaccines and vaccination strategies. Subsequently, we will be able to advise the Ministry of Health whether specific vaccines or booster vaccinations should be given in the susceptible groups identified. Also, the current vaccination schedules can be evaluated more thoroughly.

4.8.4 Planned activities

1. Comparison of vaccination with *P*<sub>WCV</sub> to *P*<sub>ACV</sub> by measuring B-and T-cell memory responses against pertussis and other antigens co-administered with the DTP-IPV-Hib vaccination.
2. Comparison of memory responses of vaccinated individuals with pertussis-infected individuals

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This project is closely linked to the "Pertussis immunology project", "Pertussis project", "Immune surveillance project" and SOR projects "Immune pathways in vaccination", "genomic analysis of pertussis", and "Host response to RSV".
4.8.5 Planned products

In the pilot phase of this project, a network with people to be able to recruit children to participate in the study with persons from the Spaarne Hospital in Hoofddorp and the WKZ/UMC has already been established. This will possibly be further developed with researchers from abroad. Furthermore, the project is expected to provide techniques which could be used to more thoroughly evaluate the immune status of Dutch populations. Moreover the project will lead to reviewed publications and possibly a PhD thesis, which will be written by a co-worker in collaboration with Dr. R.H. Veenhoven (Hoofddorp) and Prof. Dr.E.A.M. Sanders (WKZ/UMC).

4.8.6 Foreseen follow-up

A better understanding of the persistence of memory immunity induced by vaccines is likely to lead to a more rational choice of vaccine formulations and schedules to provide more sustained long-term-protection in the population. The project explores techniques which can be used to measure cellular immunity to several other pathogens as well. It will improve the evaluation of the national immunization program. The knowledge generated allows us to better substantiate the use of modern vaccines and vaccination strategies. For the DTP-IPV-Hib vaccine it would be possible that advisement about the need for adding factors stimulating the innate immune should be given. Subsequently, we will be able to advise the Ministry of Health whether specific vaccines or booster vaccinations should be given or not. The development of tools to measure T- and B-cell memory will facilitate the identification of groups with insufficient immunity and allow a rational adjustment of the vaccination program.

4.9 S/230446 B. pertussis Adaptation to Vaccination, Dr. F.R. Mooi

4.9.1 Motivation

Bordetella pertussis is the primary agent of whooping cough or pertussis, a respiratory disease that is most severe in infants and young children. Widespread vaccination of young children has significantly reduced morbidity and mortality. Nevertheless, pertussis remains an endemic disease and is one of the major causes of vaccine-preventable deaths today. According to World Health Organization estimates, 45 million pertussis cases with approximately 409,000 deaths occur every year worldwide. Disappointedly, the introduction of new, acellular, pertussis vaccines in the 1990s has not resulted in a significant decrease in the pertussis incidence.

We have strong evidence that a distinct lineage, comprised of a group of highly related (P3) strains, is spreading globally and causing epidemics. A hallmark of the resurgence of pertussis is a shift in the age-specific incidence towards older age categories and we have found that this shift is associated with the emergence of P3 strains. Recently vaccinated children are well protected against pertussis, and we hypothesize that the P3-lineage harbours adaptations which increase transmission by partially immune hosts. Thus, we propose that waning
immunity and pathogen adaptation act synergistically and both contribute to the resurgence of pertussis.

4.9.2 Aim of the project

The ultimate aim of this project is to elucidate the causes for the persistence and resurgence of pertussis in vaccinated populations. This knowledge will provide a rational basis for the adaptation of vaccines or vaccination programs. Aims addressed in this project are:

- To identify additional adaptation found in the P3-lineage (e.g. those distinct from polymorphism in the Ptx promoter).
- To study the role of adaptations observed in P3 strains in naive and vaccinated mice. We will test the hypothesis that the adaptations confer a selective advantage in hosts with low, waning, immunity.

4.9.3 Strategic and innovative aspects

The comparison of the genomes of pre-epidemic and epidemic strains is unprecedented. We are in a unique position because the P3-lineage has been identified by us only. Further, few institutes have such a well-defined B.pertussis strain collection as the RIVM. Finally, the science of deducing complex phenotypes from whole genomes is a new field with great promise for public health. This field has received a significant impetus from recent technical developments which allow the sequencing of a complete bacterial genome within 14 days at reasonable costs.

4.9.4 Planned activities

1. Identification of P3-lineage specific loci.
   Micro-array data have revealed other differences between P1 and P3 strains (A. King, unpublished data). Also, pulsed-field gel electrophoresis typing has confirmed the distinctiveness of the P3 lineage. Therefore, our first aim is to identify additional (potential) adaptations found in the P3-lineage. The complete genome sequence of a pre-epidemic (P1) and epidemic (P3) strain will be determined using a recently developed technology which allows the sequence of a bacterial genome to be completed in 2 weeks at reasonable costs.

2. Analyses of P3-lineage specific loci.
   We anticipate that not all identified P3-lineage specific loci will be relevant or can be studied. Therefore, the following decision tree will be used to select a limited number of P3-lineage specific loci for further study.
   I. The locus codes for a virulence factor, surface exposed antigen, or is involved in the regulation of these structures.
   II. The locus is immunogenic and expressed in humans.
   III. The locus is required for infection in the mouse model.

3. Analyses of P1 and P3 strains in a mouse model for waning immunity.
   The two strains of which the genome has been sequenced will be analyzed in a mouse model for waning immunity.

4. Analyses of isogenic strains in the mouse model.

14 related projects are: "Molecular epidemiology and surveillance of pertussis, Bacterial meningitis", "Pertussis immunology", "Identification of B.pertussis escape mutants with micro-arrays", "Host response to RSV and B.pertussis".
The experiments described in [3] will be performed with the two strains of which the genome has been sequenced and which are expected to differ at many loci. The individual role of a limited number of P3-lineage specific loci will also be delineated in the mouse model by constructing isogenic strains.

4.9.5 Planned products

- A number of peer reviewed publications and a PhD thesis will be written.
- Further, this work will provide the first genome sequence of a recent \textit{B.pertussis} isolate. This may result in the identification of novel vaccine candidates. DNA markers identified by this work will give an important impetus to the study of the (global) epidemiology of pertussis.
- Finally, elucidating pathways used by \textit{B.pertussis} to evade host immunity, be it naturally acquired or vaccine-induced, will open new avenues to curb the disease pertussis.

4.9.6 Foreseen follow-up

The science of deducing complex phenotypes from whole genomes is a new field with great promise for public health, and thus for the RIVM. The identification of factors which contribute to the persistence of \textit{B.pertussis} in vaccinated populations allows the rational adaptation of vaccines or vaccination programs. E.g. our preliminary results suggest a crucial role for Ptx in persistence of pertussis. If confirmed by a more comprehensive analysis of the P3-lineage, this suggests that increasing Ptx antibody levels in the human population will reduce the pertussis burden.

4.10 S/330116 Ticks: Trojan horses with new surprises, Dr. H. Sprong

4.10.1 Motivation

There are indications for increased prevalence of the bacterium \textit{Rickettsia helvetica} in the Netherlands. These pathogens are maintained in natural cycles involving mammals and ticks. Ticks live on animal and human blood and are important vectors of diseases such as Lyme disease. \textit{Rickettsia helvetica} was recently identified in European sheep ticks all over Europe. In our annual surveillance of tick-pathogens we have consistently identified \textit{R. helvetica} in a high percentage of ticks over the last 5 years. The prevalence of \textit{R. helvetica} was comparable to that of \textit{Borrelia burgdorferi} (Lyme disease) and peaked up to 65% in certain areas. Human infections with \textit{R. helvetica} have not been reported in The Netherlands, most likely because of unawareness and unspecific flu-like symptoms. These findings raise the question whether \textit{R. helvetica} exposure through tick-bites constitutes a risk to human health. In this project research will be conducted to investigate if diseases caused by \textit{R. helvetica}, are an emerging risk to public health.

4.10.2 Aim of the project

The general aim of the project is to setup and implement molecular and serological assays for the detection of \textit{Rickettsia} species in ticks and human material.

The specific objectives are:
1. Determine the pathogenicity of *R. helvetica* infection after a tick-bite in a cohort of persons with recent tick exposure.
2. Determine the presence of different Rickettsia species in the Dutch tick population.
3. Determine whether parts of Rickettsial genomes have recombined with the tick genome.
4. Determine the prevalence of *R. helvetica* infections in the Dutch population.

4.10.3 Strategic and innovative aspects

RIVM-CB has the task to monitor current and emerging infectious diseases. An increasing number of spotted fever Rickettsiae species have been associated with human diseases and may pose a threat to public health. At present no *R. helvetica* specific assays are commercially available. Tick-borne diseases like *Borrelia burgdorferii*, the Lyme spirochete are emerging in the Netherlands so it is essential to be actively involved in research regarding rickettsial infections. The extraordinary finding of *R. typhi* and other rickettsial DNA in Dutch ticks will undoubtedly have serious consequences: Either as (re) emerging zoonoses or as a potential source for virulent genes for currently non-pathogenic microorganisms in ticks.

4.10.4 Planned activities

The project can be divided in 4 main activities:

1) Isolation of Rickettsiae species from the Dutch tick population

For the detection of Rickettsiae in ticks 16S RNA sequences are amplified by PCR, and subjected to Reverse Line Blotting or sequencing. Attempts will be undertaken to isolate *R. typhi* from ticks by cultivation in mammalian cells. In parallel, *R. helvetica* will be isolated from Dutch ticks and cultivated in mammalian cells for the generation of *R. helvetica*-specific antigens.

2) Detection of antibodies to Rickettsiae in the Dutch patients

The second step is to develop and implement *R. helvetica* specific serological assays. Validation of the final assays will be done with sera from our routinely used serological assays for the detection of antibodies to different rickettsia species and in collaboration with partner laboratories in Europe. When specific techniques are established a unique biobank of serum samples from a prospective tick study where people where included with a tick bite who visited the general practitioner will be tested.

3. Molecular identification of different Rickettsiae species

Several molecular targets for the sensitive and specific PCR amplification of different rickettsia species need to be established. Two essential and independent genes will be selected, and a PCR based technique will be set up.

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15 This project is related to V/210690/01/SO Infectieziektebestrijding: ondersteuning en signalering, S/232101/01/AA Bioveiligheid, V/600000/01/AE: Virale diagnostiek, S/230126/01/PP: SOR-project Proteomics for population screenings, V/330021/01/TZ: Landelijk tekenbeet onderzoek, V/330160/07/TE: tekenoverdraagbare aandoeningen (VWA)
The different Rickettsiae genospecies in the Dutch tick population will be determined by Multi Locus Sequence Typing using Bionumerics. Finally, the prevalence of the different Rickettsia species in the Dutch tick population will be determined.

4. Lateral gene transfer between Rickettsiae and ticks
Similar approaches as described in Hotopp et al., 2007 will be used to look for lateral gene transfer: Fluorescence in situ hybridization with fluorescein-labeled probes of Rickettsia 16S RNA and other sequences should reveal their integration in the banded polytene chromosomes of ticks by fluorescence microscopy. A complementary approach for the (near) future is to obtain full access to the genome database of *I. scapularis*. Using BLAST searches with Rickettsial sequences on full-length sequences of the (partially) assembled *I. scapularis*, will allow us to see whether genetic integration occurred between Rickettsiae and ticks.

4.10.5 Planned products
1. Development and implementation of serological test for *Rickettsia helvetica* and molecular techniques for the detection of Rickettsia species in ticks and tissue samples at the RIVM, resulting in several standard techniques and assays for the detection of *Rickettsiae* in the future.
2. “Vital knowledge” concerning the prevalence and mechanisms of (re-)emerging zoonoses.

4.10.6 Foreseen follow-up
This project will have benefits for the RIVM and the public health services in the knowledge of a field that have been reported as emerging in Europe. Aim of this project is to develop and implement assays to be better equipped to study these emerging bacteria.
We try to implement the serological assays in ongoing SOR research regarding the development of proteomics based techniques because this system has enormous potential to be used as a tool to screen for many types of clinical syndromes or outbreaks.

4.11 S/340002 Effects of paracetamol on vaccination, Dr. C. M. Janssen

4.11.1 Motivation
In many European countries paracetamol is used prophylactically to reduce pain and fever associated with vaccination as a routine. Indications that paracetamol has immunotoxic effects have emerged. Recently published results suggest a negative influence on vaccination response in infants that were prophylactically administered paracetamol prior to vaccination to prevent fever while such effects in adults that received revaccination were less evident.
In animal studies paracetamol suppressed several immune parameters. There are a number of potential mechanisms whereby the frequent use of paracetamol might influence the immune system.
It is unlikely that producers of paracetamol will invest in evaluating potential adverse effects of paracetamol. However, if proven, such effects of paracetamol are highly relevant for health authorities who advise on the use of paracetamol as a prophylactic measure for vaccination-induced adverse responses, especially for children.

4.11.2 Aim of the project

The aim of this proposal is to investigate potential adverse effects of paracetamol in human volunteer studies and experimental models in mice, using DKTP and influenza vaccination responses as read out. Special attention will be paid to the risk of respiratory allergy and asthma as a result of interference with regulatory T cells that alter the quality of immune responses to infectious agents.

4.11.3 Strategic and innovative aspects

The innovative nature of this proposal lies in the new perspective on the use of paracetamol as an antipyretic. The potential immunosuppressive effects of this drug may, however, result in increased susceptibility to infections, may lower the efficacy of vaccination, and may lead to an increased risk of allergy, especially when applied shortly before active immune processes are induced. The outcome of the project will be informative for proper advice relating to vaccination procedures, especially in children.

4.11.4 Planned activities

The project consists of the following activities:

- investigation of effects of paracetamol on a bacterial and a viral vaccination in human (children and adults) volunteer studies;
- Mechanisms of action of paracetamol will be studied using spleen-cells of naïve mice or cell-lines.
- Effects of paracetamol will be analysed in vaccination models in the mouse, one bacterial vaccine and one viral vaccine;
- the information yielded by these animal studies will be complimentary to the human studies in order to shed light on potential mechanisms, to thus achieve the most reliable conclusion on the potential effect of paracetamol.

4.11.5 Planned products

The following product are foreseen:

- the yield information will be shared with health bodies such as the Dutch Health Council;
- peer review publications;
- a PhD thesis;
- (inter)national symposium

4.11.6 Foreseen follow-up

The information yielded by this project will form a basis for advice regarding the application of paracetamol in conjunction with vaccination, which is in many other countries than the Netherlands the current routine for children, and is considered in the Netherlands. The information will be fuelled to health bodies such as the Dutch Health Council.
Based on the outcome of the project, an (inter)national symposium will be organised with a view on further dissemination of the outcome in the scientific and regulatory world.
The significance of chronic diseases is growing, not the least for policymaking at the local and national level. Also from an international point of view, public health issues like chronic diseases and lifestyle are an important research subject. The possibilities of interventions need to gain more attention, because much knowledge is not sufficiently implemented. Specific subgroups of citizens need special attention, or public healthcare. Public health and cure begin to get more intricate relationships; for both areas the responsibility of citizens for healthy behaviour increases. Food, obesity, diabetes, cancer, screening and outcome of care are important topics. Cooperation between sectors already takes place and the interest of this theme will grow and more expertise within RIVM is needed.

This theme is divided into two programs: healthy ageing and chronic disease model.

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5.1 S/260126 Lifestyle from Childhood to Adolescence, Dr. A.H. Wijga

5.1.1 Motivation
It is well recognized that the chronic disease patterns we observe in today’s adult population have their origin in childhood environment and lifestyle. The current rapid changes in lifestyle and environment will unquestionably result in the development of different disease patterns in future. Close monitoring of newly evolving disease patterns is possible through long-term follow-up of the birth cohort studies that have been started all over Europe over the last decades. RIVM is one of the participants in such a form of data collection, the PIAMA study (Prevention and Incidence of Asthma and Mite Allergy). In the PIAMA study, 3500 children have been followed from before birth (1996/1997) up to the age of 8 years, when data were collected for the last time (2004/2005). The period between the ages of 8 and 14 is a period of critical changes and may be crucial for the development of lasting life style habits and their impact on the development of a multitude of chronic diseases. Very little is known on the process of changes in this stage of life, when and how they occur and what determines children’s choices and preferences. With respect to asthma too, puberty is an important period about which we know and understand too little.

5.1.2 Aim of the project
The aim of this project is to investigate changes between the ages of 8 to 14 years in life style, nutrition, physical activity and health related attitudes and behaviour that are relevant to the development of chronic diseases, such as diabetes, cardiovascular disease and asthma. Health outcomes that will be studied include asthma, other allergic diseases (such as eczema and hay fever) and overweight. We will specifically focus on high risk groups by identifying determinants, such as child and family characteristics, life events and conditions that predict the development of unhealthy life styles.

5.1.3 Strategic and innovative aspects
A longitudinal study, following children from pre-birth into puberty and collecting data on a great number of life style and environmental factors, has not been conducted in the Netherlands before. We will have unique data on the development of lifestyle and chronic diseases in children from birth into adolescence. It will show us how lifestyle and behaviour develop in a crucial stage of life and how they influence the development of body weight and chronic diseases. We will also be able to identify sub-groups of children who are at high risk to develop a lifestyle that makes them vulnerable for the development of chronic disease. In the international scientific community, birth cohort studies

16 The project proposed here is a continuation of the PIAMA birth cohort study that started in 1996 as a joint project of RIVM, Utrecht University (IRAS), Erasmus MC, UMC Groningen, University of Groningen and Sanquin Research, Amsterdam. The PIAMA study is partner in the European ‘Ga2len network of excellence’ work package on ‘birth cohorts’
with such a long follow-up are highly valued and the international position of RIVM may well benefit from having such a birth cohort.

5.1.4 Planned activities

1. Follow the PIAMA children from their primary school into their secondary school period and into puberty.
2. Propose additional data collections when the participating children are 11 and when they are 14 years old (in 2007/8 and 2010/11 respectively). Data collection for the present proposal will involve questionnaires for the children and their parents at age 11 on lifestyle, environment, health outcomes, determinants of health related behaviour, medication use, quality of life and health care utilization.

By establishing the questionnaire follow-up in this project, we will also be able to seek additional funding for measuring biological markers (such as for example blood pressure, carotid artery thickness, visceral fat, blood cholesterol, and glucose and HbA1c levels) in a physical examination of the PIAMA children, as we did at the age of 8 years. For the statistical analyses we will make optimal use of the longitudinal character of the data by application of different forms of repeated measurement analysis.

5.1.5 Planned products

- New questionnaire for the parents and the questionnaire for the children.
- Four papers will be published in international journals. These will be based both on data already available and on the new data that will be collected when the children are 11 years old.

5.1.6 Foreseen follow-up

New assignments from VWS will no doubt be acquired when new data on the age range 8-11-14 become available. In addition, we will be able to provide new input for VTV, JGZ, for the Jeugdmonitor and the Chronic Disease Model, based on these data. We also expect that the PIAMA-database will prove to be a valuable source of information on health questions that will come up in the future. We are now providing VWS with important data on the development of overweight in children, although the PIAMA study was originally designed at a time when the obesity epidemic could not yet be foreseen. In the same way, we expect that in the future we will be able to address a variety of lifestyle and health related questions that we cannot yet foresee now. We are confident that, in combination with the data already available, investment in follow-up of the study population with two more rounds of data collection will provide RIVM with an extremely valuable source of data for many years to come.
5.2 S/260146 Primary Prevention Research on Cardiovascular Diseases and Diabetes, Dr. ir. W.M.M. Verschuren

5.2.1 Motivation
Cardiovascular diseases (CVD) are the leading cause of death in the Netherlands, accounting for over 45,000 deaths and over 300,000 hospital admissions in 2004. Age-standardized mortality rates have declined but the number of hospitalizations has increased. The health care burden and expenditure is expected to increase further.

Diabetes is a growing public health problem. The number of persons with diabetes has strongly increased over the past decade, and at present the prevalence of diabetes is about 600,000 in the Netherlands. Diabetics have a 2-3 fold risk of developing cardiovascular diseases compared to non-diabetics.

Given this growing burden of diabetes and cardiovascular diseases, prevention is of great importance. Diabetes and cardiovascular diseases share a great number of common risk factors, and can therefore be interpreted as consequences of a common pathway. Prevention of diabetes and cardiovascular diseases is therefore a combined effort.

5.2.2 Aim of the project
  Aim of the project is to quantify the contribution of lifestyle factors (smoking, physical inactivity and selected nutritional factors) and risk factors (obesity (BMI/waist circumference), blood pressure, serum cholesterol, serum glucose) to the disease burden of cardiovascular diseases and diabetes in the Netherlands.
- High-risk approach to prevention of cardiovascular diseases and diabetes: Stratification of the population according to absolute level of risk: optimal targeting of health care resources to subgroups of the population that are at highest risk.
  We will examine the sensitivity and specificity of the presently used risk scores for identification of high-risk groups. Furthermore, we will examine whether identification of high risk groups can be improved, by adding risk factors that are simple to measure.

5.2.3 Strategic and innovative aspects
Prevalence of cardiovascular diseases and diabetes is high and will further increase in the near future. CVD and diabetes are responsible for a huge disease burden in the population, and consume about 11% of the total health care

17 This SOR project on cardiovascular diseases and diabetes is linked to the SOR proposal VGC 07, which is aimed at primary prevention research for other chronic diseases (obesity, cancer) and mortality. These two projects together, guarantee a broad scope on chronic disease prevention research. The project has a strong international bedding, we collaborate with 22 other European EPIC centres. Long-term national collaboration, based on several of our population studies, exists with universities of Utrecht, Wageningen, Amsterdam and Maastricht, and with organisations such as the Dutch Heart Foundation (Hartstichting) and Dutch Diabetic Association.
budget. Primary prevention is the answer to this epidemic. Two approaches, a population approach and a high-risk approach, complement each other. The present proposal aims to provide necessary information for public health policy. The project will yield important information, tailored to the Dutch situation. The RIVM has a unique opportunity to profile itself in this field of research.

5.2.4 Planned activities

1. Population approach to primary prevention of cardiovascular diseases and diabetes
   - Establishing an update with the linkage to the mortality register of the CBS, completing cause-specific mortality follow-up up to January 2006.
   - Preparing the dataset on morbidity, that has been obtained through linkage with the hospital discharge register in 2006/7.
   - Analyses and papers on lifestyle factors (physical activity and smoking) and morbidity and mortality from CVD and diabetes, based on Peilstationsproject and MORGEN-project.
   - Participation in writing group of EPIC-Heart and/or EPIC-Diabetes, on one relevant topic (e.g. blood pressure, anthropometry, or diet).
   - Analyses of dietary factors in relation to the incidence and mortality from CVD and diabetes.

2. High-risk approach to prevention of cardiovascular diseases and diabetes
   - Determination of CRP in the Doetinchem Study (if additional funding can be obtained)
   - Analyses will be performed on data from the Peilstationsproject Hart- en vaatziekten as well as on the MORGEN-project.
   - Sensitivity and specificity of current guidelines for cardiovascular risk management.
   - Analyses of adding new markers of risk to the SCORE risk function.
   - Exploring a risk function for cardiovascular disease based on dietary and lifestyle factors.
   - Analysis of the effect of CRP in risk stratification (if CRP measurements can be financed)
   - Analyzing the development of risk factors with ageing, based on the four repeated measurement in the Doetinchem Study, and the consequent effect on incidence of cardiovascular diseases and diabetes.

5.2.5 Planned products

- Peer-reviewed scientific papers and a PhD-thesis.
- In addition, accuracy of international risk functions, for identifying high-risk groups in the Netherlands, that are eligible for treatment of CVD risk factors, will be determined. Recommendations will be made on adjustment of risk functions, e.g. by adding other measures of risk (overweight, CRP), in order to increase the cost-effectiveness of the guidelines.

5.2.6 Foreseen follow-up

Published output is expected to play an important role in public health policy on primary prevention of cardiovascular diseases and diabetes, as well as in cardiovascular risk management. Knowledge on impact of diet, lifestyle and risk factors will increase. RIVM will participate and be more integrated in networks on chronic disease research.

Our results facilitate estimation of public health impact through the Chronic Diseases Model of the RIVM and enable RIVM to conduct better balanced cost-
effectiveness analyses through better comparing KEAs for primary and secondary prevention (treatment of risk factors). Although a project duration of 4 years is proposed, by definition harvesting of our large cohorts and related biobanks can go on for another 10-20 years.

5.3 S/260156 Healthy Ageing: Overweight/Underweight, Dr. Ir. W.J.E. Bemelmans

5.3.1 Motivation
With the ageing of the population the impact of the ‘old age’ health problems will increase. It is important to gain insight in determinants of health in older age. In recent decades the prevalence of overweight increased and overweight is associated with several diseases, such as cardiovascular diseases, diabetes mellitus type 2, certain types of cancer and musculoskeletal disorders. These diseases are highly prevalent among the elderly. However, the exact role and impact of overweight in the elderly is unclear. For example, several epidemiologic studies showed that overweight is not associated with increased risk on cardiovascular diseases in the elderly and that underweight is associated with increased mortality risk. Since both ‘healthy ageing’ and ‘overweight’ are important public health issues, it is highly relevant to study the interrelationship between them.

5.3.2 Aim of the project
To investigate the impact of overweight, underweight and weight history on chronic diseases and mortality in the elderly and on lifetime health care costs. Objectives are:

- To examine the association between overweight / underweight and chronic diseases and mortality in the elderly;
- To study the role of hormonal / physiological factors related to body weight and weight history;
- To assess lifetime health care costs (use of drugs) according to history of weight;

5.3.3 Strategic and innovative aspects
This project is innovative because it combines all relevant aspects of health impact of over- and underweight in the elderly (methodological issues, health care costs and physiological factors). There is paucity of scientific data in this field. Opportunities for collaboration with cohorts / projects from other European countries will be explored as well as possibilities for additional EU funding (KP7). Besides strategic aspects around the new scientific insights that will be gained, the project is also strategically important because of the obvious opportunities for international collaboration and exposure.

18 The project is related to other strategic research projects on chronic diseases. There are collaborations with National Public Health Institute, Helsinki, Finland; Harvard School of Public Health, Boston MA, USA; Lund University, Malmö University Hospital, Malmö, Sweden.
5.3.4 Planned activities

1. Preparation
   Recruiting PhD-student and establishing collaboration external partners.
2. Review of current knowledge about underweight, overweight and health in the elderly and examine the association between overweight / underweight and chronic diseases and mortality in the elderly. Identification of relevant physiological parameters for biochemical analyses.
3. Examine the association of weight history or voluntary weight loss on chronic diseases and mortality in the elderly. Biochemical determination of relevant physiological parameter(s). Study the role of hormonal / physiological factors related to body weight and weight history.
4. Assess lifetime health care costs (use of drugs) according to history of weight.

5.3.5 Planned products

- Peer reviewed publications
- PhD-thesis

5.3.6 Foreseen follow-up

Both the RIVM and the ministry of Health will benefit from the results. The results can be used for modelling scenarios of health impact (e.g. the Chronic Disease Model), for policy decision making (e.g. assessing priorities in anti-obesity policy measures). They will also provide a basis for further scientific research (e.g. in new round of Doetinchem cohort).
5.4 S/260166 Modelling SES Disparities in Health, Dr. H.C. Boshuizen

5.4.1 Motivation
Health inequalities in the Netherlands are large: those with a lower education have a life expectancy that is 4 year shorter than that of those with a high education. The difference in healthy life expectancy is even 15 years. The Dutch government has formulated as a target that these disparities should be reduced with 25% by the year 2020. Also the European Union has made reducing socioeconomic disparities in health a target.
The RIVM-Chronic Diseases Model (CDM) evaluates the average situation in the Dutch population. Results can not be subdivided by socio-economic group. For the particular case of smoking, a CDM version has been developed to study effects of socioeconomic status (SES) on life-expectancy. In order to answer future policy questions on effectiveness of policies to reduce socio-economic disparities, this approach needs to be extended to other life style factors and to diseases.

5.4.2 Aim of the project
The overall aim of this project is to develop methods to model effects of policies on socio-economic disparities in health. Specific objectives are:
- To model SES disparities in life expectancy, disease free life expectancy and DALE (disability adjusted life-expectancy)
- To validate the model by comparing results on disparities to results obtained from observational studies
- To further develop the model by applying it to one of the following questions:
  - Which diseases are mainly responsible for SES disparities in life expectancy and healthy life expectancy?
  - To which extent can disparities in healthy life expectancy be explained by differences in life style factors?
  - What are the consequences of the current trends in obesity and smoking for future disparities in healthy life expectancy?

5.4.3 Strategic and innovative aspects
Socio-economic disparities have become an important research topic during the past 15 years and much information has been collected during this period on socio-economic differentials in health. The project will both contribute to future

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19 The project is related to the CDM. Several regular projects use this model. CDM is also used in other projects in SOR ("Adaptable Chronic Diseases Model", "Modelling health effects of nutrition", IQARUS, DYNAMO-HIA and "Nutrition in our heterogeneous seniors") as well as of the SOR project S/210106/01. Collaboration partner will be the Department of Public Health of Erasmus Medical Centre.
disease modelling at RIVM (adding an important new aspect by looking at the
distribution of health within the population), to future policy making
(quantification of effect size makes it possible to see which interventions are
most promising), and to science (more insight in effects of using a complex
modelling approach compared to the more simple life-table type methods).

5.4.4 Planned activities

1. To agree on the definition of SES to be used in this project. Using
   educational level is a natural choice, as information on this is available in
   many data sources, but the feasibility of using additional indicators will
   be explored.

2. Modelling SES disparities in life expectancy and the effects of life style
   factors on life expectancy. To model this, data are needed on: SES-
   specific overall mortality rates or relative risks for SES on overall
   mortality; SES-specific prevalence rates of life-style related risk factors
   and their transition rates; Prevalence rates of SES. The project will
   explore how data from different sources (e.g. CBS) can be combined for
   modelling purposes.

3. Validation will be carried out by using the model to estimate which part
   of the socio-economic disparities in mortality can be explained by the
   risk factors in the model and compare this to findings of observational
   studies that present relative risks both with and without adjustment for
   the life-style factors in the model.

4. Including disease data in the model, which are: SES-specific mortality
   rates for those with the disease; SES-specific incidence and prevalence
   rates.

5. The disease-specific model will be used for answering one the following
   research questions (to be chosen during the project):
   • How large are the SES-differentials in healthy life expectancy and DALE
     according to this model, and how does this compare to earlier
     estimates? How can differences between our model results and those
     earlier results be explained?
   • What is the contribution of different diseases to the differences in life-
     expectancy, healthy life expectancy and DALE between socio-economic
     groups? How does this compare to earlier results using simpler
     methods?
   • What is the effect of current trends in obesity and smoking for future
     disparities in health?

5.4.5 Planned products

• A version of CDM that enables evaluation of SES specific
  interventions/policy, and thus enables us to answer future questions of
  the ministry of health. Parts of this version are:
    o A set of datasheets with SES specific input data for the CDM with
      documentation
    o A description of the approach
  • Several peer reviewed publications on the work carried out in the
    project.

5.4.6 Foreseen follow-up

The project will result in a version of CDM that enables us to evaluate SES
specific interventions/policy and present results of general policy for SES groups
specific, and thus enables us to answer future questions of the ministry of
health.
5.5 S/270126 Knowledge Transfer in Public Health, Dr. Ir. A.J. Schuit

5.5.1 Motivation
There is increasing scientific knowledge in factors determining unhealthy lifestyles. Also, insight into effectiveness of health promotion programs is growing. Based on both national and international experience we must ascertain that scientific knowledge does not easily find its way into practice or into health policy. Local parties, such as the health professionals of the municipality health service and local civil servants, reported to lack the knowledge to implement effective health promotion programs. The poor knowledge transfer is likely to result in the development and the introduction of ineffective, non-evidence based health promotion programs. The problem of poor knowledge transfer has been acknowledged by several parties and therefore various initiatives have already been taken to come to effective strategies and solutions. However, despite these efforts the uptake of available scientific knowledge into practice and policy is still insufficient and more research is needed to systematically identify strategies (new and already ongoing) and evaluate them on their feasibility and effectiveness.

5.5.2 Aim of the project
The general aim of this project is to develop and test strategies that improve the transfer of knowledge related to effective prevention programs into local practice and policy in order to stimulate evidence based health promotion. More specific the objectives are:

- Identify and describe determinants of the transfer and utilization of scientific knowledge in practice and policy.
- Investigate the demand and supply of knowledge within the policy and practice domain with respect to content, package, mode and essential conditions and relate the demanded knowledge to the supplied knowledge and describe the agreement and/or disagreement.
- Develop strategies to improve knowledge exchange and utilization.
- Test the effectiveness of these strategies at the local and/or national setting.
- Designing an action plan for broader implementation of strategies if proven effective.

The focus is on prevention programs related to smoking, obesity, excessive alcohol consumption and depression.
5.5.3 Strategic and innovative aspects

This study investigates ways to improve knowledge transfer and implementation of effective prevention programs from the scientific domain into the practice of health promotion and public health policy. Efficient use of knowledge will lead to implementation of the most effective and cost-effective health promotion strategies and to discontinuation of non-evidence based programs. Also insight into the conditions under which these transfer is optimized accounts for policy makers that need to support and stimulate implementation of effective interventions. This study relates very well to the new task of the RIVM regarding the implementation of health promotion programs in the Netherlands.

5.5.4 Planned activities

1. Determinants of exchange and use of scientific knowledge: We will make an overview of potential determinants (barriers and success factors) of both knowledge transfer as well as knowledge utilization in practice and policy, by a literature study and focus group interviews. Based on this information a conceptual model will developed and tested among health promotion professionals and policy makers.

2. Demand, supply and use of scientific knowledge The demand for and supply of knowledge will be assessed using questionnaires among health promotion professionals, health policy makers and researchers in the field of public health. The actual supply will be investigated from information reported in scientific journals, periodicals, policy documents websites and databases.

3. Development knowledge transfer strategies and evaluation plan We will develop strategies that can tackle the perceived and objective barriers, increase the skills, change the content, mode or package of scientific knowledge, or otherwise improve the intention to utilize scientific knowledge into practice and policy at the local and, if applicable, national level.

4. Evaluation of effectiveness strategies The strategies developed in phase 3 will be evaluated at the local, regional or national level, depending on the intervention strategies. Measurements will be performed on the individual level (knowledge, attitude, norms etc) and the organizational level (support, capacity building etc.). If the strategies prove to be successful, the theoretically expected health gain of one or more strategies will be calculated, using the Chronic Disease Model.

5. Action plan for broader implementation A plan will be drawn up for general implementation of the successful strategies for the new RIVM centre ‘Gezond Leven’. This plan will include recommendations for actions to improve knowledge transfer and implementation at the national level.

5.5.5 Planned products

- A conceptual model explaining knowledge transfer and -utilization from to practice and policy.

20 This project relates to the outcomes of two previous VTV projects. The study will be carried out in collaboration with the VU University, Institute of Health Science, and the Department of Communication of the Faculty of Social Science.
• Contribution to effective strategies to improve knowledge exchange and implementation of effective interventions
• Tailored advice to local health policy makers to obtain knowledge on effective health promotion and support implementation of this knowledge.
• Action plan for broader implementation of effective strategies.
• Five peer reviewed publications in scientific journals and professional and policy journals and a PhD thesis.

5.5.6  Foreseen follow-up

The results of this study can be directly used within the Centre ‘Gezond Leven’ to be established next year within the Division of Public Health and Health Care of the RIVM.
5.6 S/270146 Validation of Data from General Practice Registries, Dr. N. Hoeymans

5.6.1 Motivation
Governments need objective information about the health status of their people. Core indicators for describing population health are life expectancy, health expectancy, incidence, prevalence and mortality for a selection of diseases. In most countries data about the occurrence of diseases comes from health interview surveys measuring self-reported disease. Although surveys give a certain picture of the total burden of disease in a population, the observed morbidity is not reviewed by medical experts. It might be advantageous to use also data from registries in general practice (GP) that only count cases which seek medical care and are diagnosed or reviewed by a physician. In the context of the ‘Public Health Status and Forecasts’ (VTV) data of six registries in general practice are used. These register a broad range of diseases, have a long history of registration and cover a considerable practice population. However, incidence and prevalence rates achieved from several registries differ considerably. The researchers could not declare one registry as the most valid one, because all registries have advantages and drawbacks. Neither could they simply clarify this variation. As a consequence the validity and reliability of the Dutch morbidity data, which are to a large extent based on the registries in general practice, is unclear.

5.6.2 Aim of the project
The aim of the project is to increase the quality and usefulness of data from registries in general practice. Specific objectives are:
- Describe the characteristics of the GP-registries and make these public.
- Study the internal validity of the data by comparing the outcomes of the registry with patient records, owed by the GP.
- Study the external validity of the data by comparing the outcomes of the registry with other data-sources, for instance the National Cancer Registry. Knowledge about the external validity should also contribute to improvements in the registration process.
- Extract data of which the validity is known and publish data with and without adjustments for sociodemographic characteristics.

5.6.3 Strategic and innovative aspects
This project is a countrywide enterprise, in which representatives of six registries in general practice take part. Working on transparency of registration systems is a unique job, with hardly any predecessor. Our project combines consultation, audits by experts, data extraction from large databases, and data analyses. Assuring continuity and high quality of data on Dutch population health fits with RIVM’s foreseen role as coordinator of Dutch efforts to stimulate ‘Healthy Living’. The Public Health reporting by RIVM has been proclaimed to be the best in Europe; this project could be seen to go beyond that to improve

21 There will be a collaboration with several universities and other users of data from registries in general practice, like the Dutch Ministry of Public Health, the Centre for Quality of Care Research, the National Association of General Practitioners and the Dutch College of General Practitioners. The current project is related to the projects in the context of the ‘Chronic Disease Model’.
basic data collection in the field. It could contribute to international literature on validity and quality improvement in GP data collection.

5.6.4 Planned activities

1. Comparing the registries in detail. These details concern definitions of the diseases, the registration rules, information about the practice populations, and outcomes of the registration (incidence and prevalence rates of diseases).

2. Studying the quality of the data, (if necessary) proposing adjustments of the registration process, and computing improved estimates of the incidence and prevalence rates. Also in this study period, estimates of incidence and prevalence rates will be adjusted for demographic characteristics and socio-economic status.

3. Subsequently, external validity of the data will be studied. This will be done by comparing the outcomes of the general practice registry with other medical registries. Not only incidences and prevalences should be compared, but it is also important to look whether individual patient records can be traced in these other registries and whether the information match with the information in the records of the general practice. The last part of this period will be spent on formulating recommendations for the registries in general practice.

5.6.5 Planned products

- Knowledge about the validity of the epidemiological information from registries in general practice
- A series of more valid and reliable incidence and prevalence rates of the most important diseases in The Netherlands.
- A web-based system with characteristics of the registries, data extraction software, epidemiological data and publications about the internal and external validity.
- A PhD thesis that consists of a number of articles in peer reviewed journals.

5.6.6 Foreseen follow-up

The activities in the context of the 'Public Health Status and Forecast' will profit heavily from the results, Besides, GPs themselves can also take advantage of validation studies and possibly proposals for adjustments. Assuring continuity and high quality of data on Dutch population health fits with RIVM’s foreseen role as coordinator of Dutch efforts to stimulate 'Healthy Living'. The Public Health reporting by RIVM has been proclaimed to be the best in Europe; this project could be seen to go beyond that to improve basic data collection in the field. It could contribute to international literature on validity and quality improvement in GP data collection.
5.7 S/270166 Healthy Ageing & Health Care Expenditure, Dr. J.J. Polder

5.7.1 Motivation
Since health expenditures depend heavily on age, ageing of the population would pose serious budgetary problems for the health care systems in developed countries. There is strong evidence, however, that health care use will change. Not only because of the introduction of new therapies, but also because demand will change resulting from improved longevity and epidemiological changes. It matters whether ageing will be ‘pure ageing’ or ‘healthy ageing’. It was demonstrated that the expected cumulative health expenditures for healthier elderly persons, despite their greater longevity, were similar to those for less healthy persons who lived shorter. According to common knowledge health expenditure is driven by at least 4 factors: age, gender and disease; socio-economic position; proximity to death; calendar year. This latter category comprises a variety of influences as national income, technology, health care policy, individual en societal preferences and last but not least, the health of the population. For a better understanding of the dynamics of health expenditures in an era of ageing it is important to get a better grasp of the factors mentioned in this last category. From a public health perspective it is interesting to analyse the influence of health status on expenditure, for individual citizens and for population groups and cohorts. The results of such an analysis can be used to quantify the effects of healthy ageing on health expenditure.

5.7.2 Aim of the project
The aim of this project is to investigate the relation between health status and health expenditure and to develop healthy ageing scenarios of future health expenditure. Five specific objectives will be achieved in a stepwise fashion:

- To quantify the influence of health status on health expenditure for citizens of the Netherlands and the Dutch population as a whole, after correction for other expenditure drivers as age, gender, socio-economic position and proximity to death.
- To quantify the influence of comorbidity in relation to healthy ageing and health expenditure.
- To quantify the influence of birth cohorts on health and health expenditure.
- To develop a model for projections of future health expenditure, based on longitudinal and cross-sectional data and using multi-state life-table techniques.
- To develop scenario’s of future health expenditure under different assumptions of ageing and healthy ageing.

5.7.3 Strategic and innovative aspects
This proposal fills a gap in the national and international research agenda. The debate about health expenditures in relation to age and gender is blurred. There are a lot of ‘myths’ about the determinants of health expenditure and how these

22 The project is related to several SOR-projects (‘Healthy ageing: are diseases becoming less disabling’; Modelling the future of MRSA in the Netherlands; Future unrelated medical costs) and other RIVM-projects.
develop over time. One is the statement that increasing life expectancy will result in higher health expenditure. This research proposal addresses this question by the assessment of the influence of living longer in better (or worse) health. It is the first time that this analysis will be carried out for the Netherlands. As far as we know, even in Europe there has no comparable study been done.

This project is not only innovative, but has strategic implications as well. The insights can be used in national and international debates on health expenditure. In this sense the proposed study might enhance the position of the RIVM.

5.7.4 Planned activities

1. To quantify the influence of health status on health expenditure for citizens of the Netherlands and the Dutch population as a whole, after correction for other expenditure drivers as age, gender, socio-economic position and proximity to death. This objective will be addressed by cross-sectional analyses.

2. To quantify the influence of co-morbidity in relation to healthy ageing and health expenditure. In the cross-sectional analyses also the role of co-morbidity will be addressed. Information from the patient survey about self-perceived health, number of diseases and physical impairments will be combined with hospital data on diagnoses and health care use. Similar analyses will be done for long-term care.

3. To quantify the influence of birth cohorts on health and health expenditure. Longitudinal analyses of hospital will be performed for different population groups.

4. To develop a model for projections of future health expenditure, based on longitudinal and cross-sectional data and using multi-state life-table techniques. The results of the cross-sectional and longitudinal analyses will be used for the projection of future health expenditure. A simple projection model will be developed using traditional projection technique], as well as life-tables and more sophisticated methods.

5. To develop scenarios of future health expenditure under different assumptions of ageing and healthy ageing. The model will be used to quantify different scenarios of ageing and healthy ageing. We will contrast standard demographic scenarios with more sophisticated. We will distinguish between evidence-based insights and scenarios as developed in other studies and more hypothetic ‘what-if’ scenarios.

5.7.5 Planned products

- PhD-thesis.
- A series (6-7) of scientific articles published in peer reviewed scientific journals.
- Presentations of study results at national and international conferences.

5.7.6 Foreseen follow-up

The proposed project will yield new insights that will be interesting for several parties, e.g. RIVM itself, Ministry of Health, national and international scientific
groups, national and international councils and bureaus for policy, the health care sector.

5.8 S/340020 Healthy Ageing, Diet Interventions, Dr. M.E.T Dollé

5.8.1 Motivation
Healthy ageing is a clear-cut priority of public health policies worldwide. The main focus should be on extending the number of healthy years. In order to attain this goal, preventive measures are of significant importance, in particular to decrease severity and to delay time of onset of chronic diseases. Cardiovascular disease, diabetes, obesity and cancer are among the most prevalent chronic diseases in the Netherlands (Nationaal Kompas Volksgezondheid). Experimental and epidemiological evidence indicates that both diet and genetic make-up influence susceptibility to these chronic diseases and ageing itself. Hence, fundamental knowledge on gene-diet interactions in the aetiology of chronic disease is expected to provide important insight for the prevention or delay of these disorders. For this reason, we propose to investigate gene-diet interactions in relation to cancer, metabolic syndrome and its sequela both in human and in the mouse.

5.8.2 Aim of the project
The aim of this current project is to better understand molecular mechanisms that underlie ageing and associated chronic diseases in relation to diet. In turn this knowledge will be used to design diet-based intervention strategies and to identify biomarkers for monitoring (health) effects of interventions and denoting individuals at risk for developing age-related diseases. Our objectives are:

- To verify whether ageing mechanisms and age-related diseases in rodents and humans carry similarities
- To identify new potential pathways influencing disease susceptibilities
- To design, based on the associated genes and pathways in objectives 1 and 2, diet-intervention strategies
- To identify and assess potential biomarkers, denoting at risk individuals and monitoring pathogenesis and intervention strategies

5.8.3 Strategic and innovative aspects
Innovative is the combination of epidemiology, molecular biology and genetics for the development of intervention strategies that promote healthy aging. The associations found in animal models will be further studied and validated in human studies and vice versa to ensure proper associations and results via extrapolation. RIVM has, through extensive collaboration, access to a wide range of unique human materials enabling human genetic studies in all kinds of Dutch sub-populations (e.g. patients and elderly). Furthermore, RIVM has at its

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23 This project is related to the KP6 projects DIOGENES (impact of diet and genes on weight gain), and INTERACT (genetic and lifestyle factors will be related to type 2 diabetes). Within the current SOR framework this project is also related to projects “Nutrition issues in our heterogeneous seniors” (Nynke de Jong, CVG) and detection of biomarkers through proteomics (Annemiek de Vries, TOX). The project is supported by external grants from EZ/Senter IOP Genomics (IGE03009) and NIH/NIA (PO1 AG17242
disposal unique animal (and in vitro) models, including tissue banks from earlier experiments that can be further explored.

5.8.4 Planned activities

1. Association studies in human cohorts. Based on data available from literature and from our own animal studies we earmarked specific biological pathways to be further analyzed in human cohorts. We will combine the above two ongoing research activities within one new human cohort (Maastricht study, PhD study in collaboration with Wageningen University). The cohort consists of 22,000 participants, with at least 600 cancer and 600 cardiovascular cases expected.

2. Identifying new pathways Before we will be able to design useful biomarkers we need more knowledge on age-related diseases and pathologies. From our previous animal studies we have collected various tissues from mice that will now be used for identifying additional pathways involved in the development of chronic disease.

3. Intervention strategies Relevant pathways, as determined under objectives 1 and 2, may subsequently point to intervention strategies, especially when disease risk is related to differences in dietary intake (gene-diet interaction).

4. Biomarker development Analogous to objective 3, identified critical pathways under objectives 1 and 2, should also suggest potential biomarkers for identifying at risk individuals, pathogenesis and intervention results. First results in this respect are our ongoing studies with human diabetes type 2 patients supplemented with low doses of antioxidants, which appeared to have a positive effect on serum parameters of oxidative stress and inflammation.

5.8.5 Planned products

- Knowledge on the interaction and relation of biological pathways with food intake and healthy aging.
- Maintenance of general knowledge on genetic epidemiology, animal pathology, genetic toxicology to sustain future expert advice.
- Identification of high risk sub-populations for important chronic diseases
- Proposals for intervention strategies.
- Future expert advice to regulatory entities (VGP/VWA) on individual, tailored advice or intervention strategies with the aim to reduce medical costs.
- Peer reviewed scientific papers.
- A workshop will be organized on gene-diet interactions.
- PhD thesis on gene-diet interactions in relation to the metabolic syndrome and cardiovascular disease in collaboration with Wageningen University.

5.8.6 Foreseen follow-up

- Intervention strategies for Dutch population to ameliorate ageing by reducing chronic disease, which will ultimately lead to reduction in health care costs.
- Scientific community will benefit through knowledge on mechanisms on chronic diseases and more in general on the ageing process itself.
- Ministry of Public Health and Sports will be supported on science-based decisions and advice on healthy food policies.
Integration into new activities at the European level concerning "healthy people"
6 Medicines and Functional Foods (MFF)

Medicines and novel foods are more and more tied up. RIVM needs to acquire more knowledge and skills in this field. Simple answers of 'right or wrong' do not satisfy. A shift appears from risk assessment to risk-benefit approach and chain approaches. The importance of understanding system functions in care is growing. Changes can only effectively be met when 'consumer behaviour and understanding' get proper attention.

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6.1  S/340040 Chronic Drug Use and Autoimmunity, Dr. ir. R.J. Vandebril

6.1.1  Motivation

Individual autoimmune diseases are generally perceived as relatively uncommon. Yet, when all autoimmune diseases are combined, the estimated prevalence is considerably higher (3-5 %). Autoimmune diseases can be severely incapacitating, underlining their importance to public health. Notable examples of autoimmune diseases include type-1 diabetes mellitus, rheumatoid arthritis, and systemic lupus erythematosus. Drug-induced autoimmune-like disorders are of a major concern, and as idiosyncratic reactions often reason for withdrawal from the market or restricting their use. Drugs may be easily identified as causative factor in case there is a direct association in time of reactions with the use of the drug, and subsequent improvement after withdrawal.

6.1.2  Aim of the project

The aim of this proposal is to elucidate the role of anti-inflammatory drugs in the increasing prevalence of autoimmune diseases. The specific objectives are:

- to establish epidemiologic associations of long-term drug use exerting anti-inflammatory activity with chronic inflammatory autoimmune diseases
- to establish the causality of associations evident from the epidemiological studies using ex-vivo in-vitro analysis of immune parameters in humans and in animal models for autoimmune disease.

6.1.3  Strategic and innovative aspects

There is increased chronic use of preventive therapy (antihypertensives, cholesterol lowering agents) to reduce the risk of cardiovascular events, diabetic exacerbations and the like. Little is known about the long-term immune effects of these drugs, although there is information that some of them have immune-modulating effects. The research question whether their long-term use is associated with immune effects is relevant both from a safety and public health perspective. The innovative nature of this proposal lies in the study of long-term effects in terms of facilitation of autoimmune diseases according an epidemiologic approach, and the assessment of causality. The latter will be done by evaluation of immunologic parameters both in humans and in animal models of autoimmunity in which experimental drug treatment is applied.

6.1.4  Planned activities

1. Assessment of epidemiologic associations of chronic inflammatory autoimmune diseases with drug use. We will investigate epidemiological associations between the long-term use of anti-inflammatory medication using the Doetinchem Study by investigating.

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24 This project is related to the projects: “Voedselovergevoeligheid bij kinderen”, “Gezondheidsbevorderende voedingsmiddelen”, “Advisering kennisbasis sensibiliserende stoffen”, “Specifieke gevoeligheid van kinderen”, “Beoordeling van geneesmiddelen”

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2. Individuals suffering from autoimmune diseases. These will be compared to matched controls with respect to their use of medication.

3. Serum from individuals within the Doetinchem Study for standard autoimmune markers. Serum from these individuals is collected at several time points, it is possible to study the kinetics of alterations of autoimmune markers, and link these to the occurrence of autoimmune diseases.

4. Assessment of causal relationship of associations evident from the epidemiological studies using animal models for autoimmune disease. To this end two specific animal models that represent a wide spectrum of autoimmune conditions will be used to study the effect of drugs on the development of autoimmunity.

6.1.5 Planned products

- Knowledge on (auto)immune side effects of long-term drug use, relevant for evaluation of drugs, including risk-assessment and risk-benefit evaluation.
- Peer reviewed publication on: prevalence of autoimmune disease in the Doetinchem Cohort, values of autoimmune markers in the Doetinchem Cohort, the association of drugs and autoimmune diseases, the association of drugs and values of autoimmune markers, and effects of drugs in experimental models of autoimmunity.
- A PhD thesis on the impact of long-term use of drugs with immunomodulatory activity on the development of autoimmunity is envisaged.
- A Workshop on the impact of long-term use of drugs with immunomodulatory activity on the development of autoimmunity will be organised (participants: scientists, regulators)

6.1.6 Foreseen follow-up

Besides the scientific community, especially scientists interested in adverse effects of drugs including immunotoxicity, a main beneficiary of the outcome of this project will be the Ministry of Public Health and Sports, as it may eventually support policy decisions on post-marketing surveillance of drugs (in the US legislation on mandatory post-marketing surveillance is being considered). Also the RIVM Centre for Biological Medicines and Medical Technology, that performs assessments of medicines for the Dutch and European market and is involved in core (European) procedures for the authorization of medicines, and the RIVM Centre for Public Health Forecasting, that supports national and international health policy makers by providing and disseminating insight into the Dutch health status, its determinants and the consequences of ill health and about possible health futures will benefit from the outcome of this project. Pharmaceutical industries may use the knowledge gained to select better drugs and design post-marketing surveillance strategies.
6.2 **S/350030 The Food Pharma Interface, Dr. C.J.M. Rompelberg**

6.2.1 **Motivation**

With the market introduction of functional foods and dietary supplements, consumers are stimulated into a self-medication movement. If they actively want to improve health, they can choose between different health promoting strategies, like the traditional diet approach, functional foods, dietary supplements and (lifestyle) drugs. To make this choice, consumers have to rely on information provided by health professionals or focused consumer education centres. Unfortunately, the sources of information do not provide an overall picture of all approaches as their knowledge is mainly restricted to either the traditional diet (dietician/Dutch Nutrition Education Centre) or pharmaceuticals (physician/pharmacist). An overview of the complete field of health promoting strategies, including functional foods and dietary supplements and their possible interactions with other foods, dietary supplements and drugs, is unavailable. Nevertheless there is a clear need for information on the food-pharma interface as identified through consumer interviews, surveys among dieticians and lectures for health professionals on this topic. Especially information on claims, safety, efficacy and product handling of functional foods and dietary supplements, and alternated or combined use with pharmaceuticals is needed.

6.2.2 **Aim of the project**

Aim of the project is to combine expertises in (functional) foods, dietary supplements and pharmaceuticals and to develop relevant tools on the food-pharma interface, which can be used to inform consumers and professionals and to answer future questions of policy makers. Specific objectives:

- A prototype of a “food – pharma” database, which is suitable as basis for a (future) website (information platform) on food-pharma issues. The database will consist of part A and B. Part A aims to give an overview of available food and pharma health promoting strategies (traditional diet, functional foods, dietary supplements and pharmaceuticals) per disease or risk factor. Part B aims to give an overview of interactions between foods, functional foods, dietary supplements and pharmaceuticals by combined use of these products for the same and different indications.
- A risk-benefit or effectiveness methodology to quantify the overall health effect at population level per food/pharma strategie and to compare different strategies with each other.

6.2.3 **Strategic and innovative aspects**

The innovative nature of this research is the focus on both food and pharma and its interface (functional foods and dietary supplements) and the goal to put the information together and to evaluate (by risk-benefit/effectiveness analysis) them against each other. The database can be used to give information on the

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25 This project builds on previous and current experience with (functional) foods, dietary supplements and drugs within RIVM. Collaboration partners are the University of Utrecht and University of Wageningen.
interface that neither the Dutch Nutrition Education Centre, the Dutch Consumer Association, the pharmacies, the health promoters themselves nor the food and drug manufacturers do fill at the moment (as they mostly provide information for their particular area of expertise). This project will give the opportunity for (inter)national positioning in the field of risk-benefit/effectiveness methodology and the field of food-pharma.

6.2.4 **Planned activities**

**Objective 1:**
1. An exploratory study on the needs and possibilities with regard to the food-pharma database. Relevant parties will be interviewed to identify the needs of consumers and professionals on the food-pharma interface. Based on the results, relevant items for the database will be selected.
2. Inventory of available food and pharma data to fill the database. Data will be collected from hand books, product labels, patient leaflets, relevant internet sites, scientific literature, and, if available, from relevant existing databases RIVM.
4. Critical evaluation of available food and drug data (Go-no go decision: Are there sufficient data to continue with filling of the database (part A and B)? If the answer is no: the project will end in December 2008. If the answer is yes (there are sufficient data to fill part A and/or part B of the database): the project will be continued in 2009 with further filling of the database.
5. Further filling of the database.

**Objective 2:**
1. Explorative phase: inventory of available methods on risk benefit analysis or effectiveness which can be used to answer questions like "Which food/drug- treatment is (most) effective on a population level for the disease/risk factor of interest?"
2. The most promising/suitable method, will be further developed, using a case example to be selected from the food-pharma database.

6.2.5 **Planned products**

- Food-pharma database, which can be used as basis for a website/information platform on the food–pharma interface.
- Method to compare food-pharma strategies at population level.
- Vital knowledge and network on food-pharma. This will be important for future assignments.
- Presentations of results at (inter)national conferences/workshops.
- Peer reviewed publications, reports, brochure and a PhD-thesis.

6.2.6 **Foreseen follow-up**

For the future it is anticipated that both the prototype of the database and the risk-benefit/ effectiveness method can be used for new assignments. The usefulness for new assignments is expected to be high, especially for the Ministry of Welfare, Health and Sports, the Dutch Nutrition Centre, the Dutch Consumer Association and also pharmacists and dieticians associations. The database can be used to set up an information platform for consumers and health professionals. The risk-benefit/effectiveness method as proposed can be used as decision support tool to decide which food/pharma interventions can be recommended for a specific population in the treatment/prevention of a disease or enhanced risk factor.
6.3 S/360001 Novel in vitro test for pertussis toxin, Ing. A.M. Akkermans

6.3.1 Motivation

Whooping cough (pertussis) is an acute respiratory infection, caused by Bordetella pertussis. It manifests as a protracted cough illness. Pertussis toxin (PTx) in its detoxified form (dPT) is an important component of both whole cell and acellular pertussis vaccines (ACVs). Different ACVs comprise different combinations of putative protective antigens of B. pertussis, but they all contain dPT as protective antigen. For safety reasons, it is imperative to ensure that the quantity of residual PTx in vaccines does not exceed permissible levels. Therefore, each batch of pertussis vaccine is subjected to extensive safety testing in animals: the histamine sensitization test. However, presence of residual PTx causes major distress, or even death, in the experimental animals. Development of an in vitro method is urgently needed.

So far, several in vitro assays to detect PTx have been developed, but correlation of the functional in vitro test with the in vivo tests might remain poor. In the present research project, we propose to develop an alternative in vitro method, based on the published knowledge that PTx induces phenotypic changes in different cell types. We hypothesize that the phenotypic changes in cells induced by PTx are preceded by an altered gene expression profile: specific genes are either up- or down regulated. We aim to analyze these differential gene expression profiles using microarray technology. In turn, these marker genes may form the basis of a novel alternative in vitro test to quantitatively analyze PTx.

6.3.2 Aim of the project

The aim of the project is to develop an in vitro method to detect pertussis toxin in final vaccine formulations. To reach this goal, the following specific objectives of the project need to be achieved:

1. Identification of suitable cell lines, demonstrating phenotypic changes upon PTx exposure
2. Identification of candidate marker genes
3. In-house validation of the in vitro method

6.3.3 Strategic and innovative aspects

- The –omics based in vitro method will be functional for both isolated PTx and final vaccine products. This proof of functionality is essential for acceptance by regulatory bodies.
- The role of –omics technologies in potency and safety testing of biological medicines, such as vaccines, is almost negligible and research in this area is only in its infancy. The outcome of this research project might enhance the use of –omics technologies in

26. Related projects are: SOR project S/340010 ‘Toxicogenomics in risk assessment’ and EU-project EU project E/360040 ‘Europese Vrijgifte’.
vaccine potency and safety testing for other vaccines besides pertussis vaccines.

- The -omics based in vitro method might serve as a scientifically sound reference method for validation of possible future (cheaper) methods.
- This project will strengthen RIVM’s position in future expert advice to regulatory entities.
- The project helps BMT to get in contact with academia in the pharmaceutical field.

6.3.4 Planned activities

The research proposal defines three phases:

Phase 1 (Month 1 – 24): Identification of candidate marker genes in exposed cell lines

We will select a suitable cell line based on a thorough literature study. Besides sensitivity to PTx, suitability for validation versus the classical mouse model will also be taken into account. Selected cell line(s) will be exposed to pertussis toxin per se or final vaccine product spiked with a dose-range of pertussis toxin. Phenotypic changes in metabolism or cell growth will be used to design the test model. Secondly, cells will be exposed to the test “vaccines” in order to generate gene expression profiles using microarray technology. From these expression profiles, candidate marker genes will be identified by performing extensive data analyses.

Phase 2 (Month 25 – 36): Pre-validation of a subset of candidate genes.

Sensitivity and specificity of (a subset of) the candidate marker genes is determined using microarray technology. In this phase we will analyse how far the number of genes to be tested can be reduced without affecting the outcome of the assay. In this phase a choice is foreseen between qPCR and microarray technology.

Phase 3 (Month 37 – 48): In-house validation.

The new in vitro method will be subjected to in-house validation. This includes determination of specificity, sensitivity, precision, and robustness. Furthermore, correlation with the classical in vivo test method will be determined using available in vivo data, derived from on-going batch release testing. BMT has ample experience in validation of methods (ISO17025 accredited).

6.3.5 Planned products

- A high specific alternative in vitro method to detect pertussis toxin, preferably in final vaccine formulations, to replace HS testing. HS testing is one of the few animal models in quality control of human vaccines with lethality as endpoint.
- Improved expertise to be used in advice to regulatory entities.
- Endorse the scientific position of RIVM in the EC and other international frameworks.
- At least two scientific papers in peer-reviewed journals.
- Improved opportunities to secure externally-supported projects.

In addition, it will confirm the (international) position of the RIVM (and the Netherlands) as a leading partner in innovative testing and alternatives for animal testing, increasing our access to European grants and consortia. Furthermore it will facilitate future cooperation with academia, as well as ensure
cooperation with national laboratories of the OMCL network and vaccine producers.

6.3.6 Foreseen follow-up
If successful, additional inter-laboratory validation in cooperation with interested parties (e.g. ECVAM) is to be expected. Finally, this project can contribute to the EU goal of replacing vaccine (safety) tests using laboratory animals by fully in vitro test systems.
6.4 S/360003 Carcinogenicity of growth factors, Dr. J.W. van der Laan

6.4.1 Motivation
Carcinogenicity testing of pharmaceuticals is mainly done through life-time exposure studies in rodents. These ‘assays’ frequently end up with so called false positive results and as such do not represent the human situation. Still though, special concerns exist when human recombinant protein hormones or analogues thereof respond positively in these carcinogenicity tests. During the development of recombinant insulin-analogues the insulin AspB10 (but not human insulin) appeared to induce mammary tumors in rats. This result may identify a potential for humans using new insulin analogues, and very recently some epidemiological data obtained from human studies is signaling for such a risk. With respect to determining carcinogenic features of human (recombinant) hormones or analogues, the testing strategies as requested by regulatory authorities in global guidelines are inadequate. Therefore, more mechanism-based methods are needed that can identify true compounds which are at risk to humans.

6.4.2 Aim of the project
The aim of this project is to define strategies for assessing the carcinogenic risk of recombinant human growth factors and their analogues. For this, we propose to use insulin analogues as a model compound in relation to mammary gland carcinogenesis. The specific objectives of the project are:
to analyze in vitro the molecular and cellular responses induced by different insulin analogues.
to determine in vivo the carcinogenic properties of insulin analogues on mammary cancer development.
to define a set of ‘signatures’ of pro-mitogenic insulin analogues using gene expression profiling.

6.4.3 Strategic and innovative aspects
There are several strategic and innovative aspects to mention:
the uniqueness of this approach is the use of in vitro (LACDR, Division Toxicology) and in vivo studies (both at the LACDR and RIVM-GBO/LUMC Toxicogenetics) integrating the pro-mitogenic and –carcinogenic effects of insulin analogues in the context of human IR and IGF1R signaling;
the integration of both in vitro and in vivo models to unravel the signal transduction pathways that are activated by insulin analogues;
a systematic analysis of gene expression profiling of different insulin analogues in the context of its biological effect under in vitro and in vivo conditions will provide better safety evaluations in the future.

6.4.4 Planned activities
specific objective 1: To analyze in vitro the molecular and cellular responses induced by different insulin analogues. We anticipate that insulin analogues may act through the insulin-receptor and/or the insulin-like growth factor receptor (IGF1R). Here we will systematically evaluate the role of IR and IGF1R in insulin
analogue signaling in a panel of human mammary epithelial cells that selectively express either the IR or the IGF1R receptor.

Specific objective 2: To determine in vivo the carcinogenic properties of insulin analogues on mammary tumor development. Ultimately we anticipate that in vitro models should be able to establish the differential activation of insulin analogues of the IR and IGF1R.

Specific objective 3: To identify specific signatures of pro-mitogenic insulin analogues using gene expression profiling. These proposed experiments will ultimately reveal the specific preference of a selected set of insulin analogues for either the IR or IGF1R. We will use IR and IGF1R human breast cancer cell lines developed under objective 1 to define gene expression (signature) profiles that can discriminate between either IR or IGF1R activation. Furthermore, we will use tumor material from objective 2, to determine the correlation between the predictive pathways activated by IR and IGF1R under in vitro conditions with the in vivo situation.

6.4.5 Planned products
Two products are planned:
- Ph.D. Thesis
- Publications in peer-reviewed scientific journals

6.4.6 Foreseen follow-up
6.5 S/370020 MAGIC: Manipulation and Administration of Medicines Given Children, Drs. D.A. van Riet-Nales

6.5.1 Motivation
The range of approved medicines for use in children is limited in number, diversity and actuality compared to those for adults and their formulation design may not be optimal. Consequently, children too often use medicines with insufficiently demonstrated efficacy, unknown safety or a poor formulation design. The European Commission has prepared new legislation meant to improve the health of the children of Europe by increasing the research, development and authorization of medicines for use in children. Despite legislative stimuli, it is not reasonable to expect approved medicines to become available for all diseases children may suffer from. This means that children will continue to be treated with unapproved medicines. Often these will be medicines for use in adults suffering from the same disease. It may hereto be necessary to adapt the dosage, dosage form, and device or to mix the medicine with food or liquid. Extemporaneous preparations are another solution. Consequently, the health of European children will be improved by acquiring increased knowledge on the principles of good manipulation of adult medicines for use in children and by establishing general guidance for development of extemporaneous preparations.

6.5.2 Aim of the project
The study aims to improve the health of the children of Europe by scientific research to the 'Manipulation and Administration of medicines for use in children'. Specific objectives:
- An inventory of the current situation with regard to (critical) quality aspects in the manipulation and administration of medicines for children of 0-12 year age.
- Risk analysis and risk reduction: Within a specified patient group or group of care takers, a risk analysis will be performed of the situation under 1 by relating the frequency of the (critical) quality aspects to the harmfulness of any resulting incompliance for the child and its environment
- Clinical trial: One of the improved formulations, medical devices or patient instructions will be tested in a clinical trial.

6.5.3 Strategic and innovative aspects27
The study is meant to explore the field of medicines for use in children, which is currently gaining increased attention from policy makers at a European and national level (VWS) next to health care professionals and Patient Organization Groups. The results allow RIVM to continue to write good quality assessment reports on behalf of MEB (Medicines Evaluation Board) in the Netherlands, also

27 The study will be performed in cooperation with the MEB, the UIPS together with the Utrecht Pharmacy Panel for Education and Research (UPPER network) and the UMCU, with special emphasis on the hospital pharmacy and the WKZ. Key experts from the European Medicines Agency (EMEA) will be involved when relevant.
for the expected increased number of applications or variations for medicines for use in children. It therewith contributes to MEB’s strategic business plan to keep its Top 5 position in Europe. The results support RIVM in its task to professionalize the Youth Health Care as it enables RIVM to inform health care professionals on problems related to the administration of medicines for use in children and the associated risk of patient incompliance. This allows professionals to better advice parents or care takers and take appropriate action, where necessary. Novel expertise in relation to medicines for use in children may lead to new assignments by VWS, WHO and others.

6.5.4 Planned activities

1. Inventory
   • Literature study
   • Enquiries amongst Dutch children and parents/care takers
   • Interviews patients, pilot enquiry, enquiries, draw up code book and quantify risks, evaluate risks for the next objective
   • Enquiries amongst health care professionals
   • Interview health care professionals, pilot enquiry, enquiries, draw up code book and quantify risks evaluate results in the interest of the next objective
2. Risk analysis and risk reduction
3. Product optimization
4. Clinical trial

6.5.5 Planned products

• Enquiries and brochures
• Medicinal drug product with improved quality of the product itself or its related medical device or its user instruction
• At least 3 scientific publications international peer reviewed journals
• PhD thesis
• Other publications (RIVM report or in national or non peer reviewed journals)

6.5.6 Foreseen follow-up

Several stakeholders will profit from the project. The results are meant to contribute to the objective of the European Commission to improve the health of the children of Europe by increasing the research, development and authorization of medicines for use in children. MEB and RIVM will profit and the Ministry of Health, Welfare and Sports will profit in relation to their interest in ‘Medicines for use in children’.
Environmental Quality and Health (EQH)

Monitoring remains vitally important for many environmental issues, like, among many others, particulate matter. Risk assessment becomes more and more important for healthy environmental conditions and economical activities. Options to choose for different behavioural scenarios and risk perception need more attention. There is a need for skills in complicated risk assessments and environmental health impact assessment. This theme Environmental Quality and Health represents the versatility of the sector MEV. However, also other sectors of RIVM may be involved in monitoring effects of the environment on health.

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7.1 S/607002 RCiERA: Research Cooperation in Ecological Risk Assessment, Dr. A.M. Breure

7.1.1 Motivation
Because recent soil and water policies are changing towards a more integral approach (e.g. substantiated in the Water Framework Directive), there is a need for integral assessment of effects on the total environmental stress on the ecosystem. This asks for the integration of ecotoxicology in ecology, resulting in a new scientific sub-discipline called stress ecology.

7.1.2 Aim of the project
The aim of the project is to develop tools to quantify the cause and effect chain in an environment where the ecological status is influenced by the presence of multiple stressors. The subjects studied will be:
- Quantification of ecological risks posed by mixtures of toxicants
- Effect of environmental stress on ecosystem structure and functioning
- Development of tools for ranking the major stresses causing environmental impacts.

7.1.3 Strategic and innovative aspects
With the present knowledge the questions of the effects of environmental stress on ecosystem composition and functioning can be answered very poorly. The proposed collaboration provides extra working power on the development of tools to answer such questions. The participants in this collaborative project are thought to be potentially relevant partners in EU projects and position themselves herewith in good starting position to obtain extra research funding.

7.1.4 Planned activities
In this section only the activities of the RIVM-funded staff are described. Radboud University will bring in the same amount of personnel, whose activities are not mentioned below.

1. Ranking stresses using food web analysis
   Expected species sensitivity distributions in relation to the impact of anthropogenic stressors will be obtained by exploring the topological behaviour of food web models. This can be achieved in several ways. For instance, biotic abiotic soil monitoring data and metabolic functions will be combined to describe the toxicokinetics and toxicodynamics at species level. Alternatively, stressors may be considered to destabilize the system in a more general sense, for instance by favouring species with certain characteristics and strategies that fit better the dynamics of a new situation at community level. The discrimination of effects of stressors will be performed by multiple regressions and generalized linear models. Using this approach it will be possible to select the environmental pressure with the highest impact, and to depict the stressor that can be influenced with the best price/effect relationship.

2. Effect of environmental stress on ecosystem composition and functioning

28 The project is a collaborative action of RIVM and Radboud University (Nijmegen). Related SOR-projects are: EIA (MEV03), Integrated Testing Strategies for Risk Assessment of Chemicals (MEV05). The project is related to several regular projects for VROM-DGM and several projects in the EU 6th Framework Research Program.
Time will be spent on concrete modelling and in-depth analysis of already available data on species composition and relative abundance of various species in aquatic and terrestrial systems. The field data will be analyzed by statistical techniques such as multivariate analysis to derive the contribution of different factors to the shape of the contribution.

7.1.5 Planned products
- Methods for integral assessments of environmental stress
- 2 PhD theses
- At least 4 peer reviewed papers per PhD student

7.1.6 Foreseen follow-up
The project will strengthen the position of RIVM in ecological risk assessment and will give it a good position for the realization of commissions in the national and European governments for the implementation of the European Water Framework directive, the European Soil Strategy and regulation of chemicals within the framework of REACH. Furthermore, the cooperation with Radboud University will result in persons educated in the scientific field where RIVM is active and therewith will act as a potential supplier of new well educated staff.
7.2 S/630001 Environmental Health: Collaboration IRAS, Dr. Ir. E. Lebret

7.2.1 Motivation
Environmental Health Impact Assessment is a core activity of RIVM in its role to serve the government with advice on complex environmental health issues. The Division of Environment and Safety (MEV) has selected a number of strategic core fields of expertise that are considered vital for the long term. For these expertise fields, we strive for further deepening of our knowledge and expertise, through organized cooperation with academic centres of excellence, i.e. the Institute of Risk Assessment Sciences (IRAS) of Utrecht University.

7.2.2 Aim of the project
The project has two main aims:

- To continue and broaden our cooperation in the field of traffic-related pollutants to the end of further and deeper understanding of relevant exposures and health effects of (traffic-related) air pollution in the Netherlands. This work will be developed along the lines of the RAPTES project.
- To increase the scope of the cooperation by joint work in environmental health impact assessment, i.e. studies on environmental disease burden and societal cost and benefits associated with environmental health problems. We aim at a better understanding of environmental health impacts and the associated uncertainties. This work will be developed along the lines of the VAMPHIRE project.

7.2.3 Strategic and innovative aspects
This project provides the opportunity to collaborate with a top ranking institute (i.e. IRAS) on environmental health. Innovative aspects of RAPTES include the hybrid approach and combined use of elements from epidemiological and toxicological study designs, along with the use of a Biosampler for collection of size-fractioned particles. The innovative aspects of the VAMPHIRE lie a.o. in the broad description of multifaceted aspects of environment health risks and impact, the structured approach to issue framing, the structured incorporation of uncertainty in the appraisal process and the structured involvement of users and stakeholders.

7.2.4 Planned activities
The planned activities are described in more detail in the RAPTES and VAMPHIRE projects. Broadly, the research cooperation with IRAS will be developed in parallel:

1. During the first year, two PhD students will develop specific work plans; start with literature review and preparation of field work.
2. During year 2 and 3 the field work will be executed, and the first results will be analysed and interpreted. After this there will be a mid-term review.

29 Related SOR-projects are RAPTES, VAMPHIRE, IQARUS and PACEHR. Furthermore, at IRAS, related projects are several PhD-studies, the Academic Collaborative Centre Environmental Medicine project on 'Hospital Admissions and GIS' and the RIVM project SMARHAGT.
3. During year 4 and 5 the field work will be continued, manuscripts and PhD-thesis will be prepared and the cooperation will be evaluated.

7.2.5 Planned products
- A series of peer reviewed publications

7.2.6 Foreseen follow-up
For the two research lines, we anticipate follow-up and add-on activities through the 7th Framework Program of the EU, and application of the developed expertise and know-how in policy support at the national and EU-level.

7.3 S/680001 Relating Groundwater + Air Quality for N, Dr. Ir. W.A.J. van Pul

7.3.1 Motivation
The presence of nitrogen substances causes severe environmental problems, like eutrophication of nature areas, a loss in biodiversity, pollution of drinking water. National and international legislation is intended to decrease the nitrogen burden to the environment. The outlook for the next decade is that nitrogen will remain a rather persistent problem.

To describe the nitrogen burden on a national scale measurements are carried out in individual compartments, i.e. air and soil. RIVM runs the monitoring networks in the Netherlands for a) the upper groundwater under nature and agriculture and b) the air quality and (wet) deposition. In general the data of the networks are designed, reported and interpreted separately, e.g. nitrate in upper groundwater and ambient ammonia concentration. By integrating measurements and modelling between the compartments a large profit is obtained in a) understanding the observed levels and trends in the compartments and b) in understanding these levels in relation to the policy measures.

The observed levels of nitrate in the upper groundwater under nature areas can be explained for 35% in terms of the atmospheric nitrogen deposition and simple soil characteristics. The atmospheric deposition is estimated based on wet deposition measurements and an empirical approach for the dry deposition. The observed relationship between nitrate leaching and the atmospheric nitrogen deposition can be improved considerably by using better estimates of the dry deposition of nitrogen. These dry deposition estimates on ecosystems can be improved by combining measurements of the ammonia concentration in air on one hand and modelling of the deposition process on the other hand.

7.3.2 Aim of the project
The overall aim of the project is to carry out an analysis of the measurements of the nitrogen components in soil and air to obtain a better explanation of the observed nitrate levels and trends.

Specific objectives are a) to explain the observed levels and the links between the levels in the networks; b) to obtain a better description of the nitrogen deposition to nature areas taking into account the vegetation characteristics; c) to extend the measurements in the network to derive a more complete
description of the nitrogen loads; d) to derive a simple method with which the groundwater leaching can be explained in terms of easily obtainable input data.

7.3.3 Strategic and innovative aspects

The project is strategic and innovative for several reasons. It is a unique integration of knowledge on measurements and models and expertise from soil science and air quality science. The explanatory power of the data from the networks is improved considerably compared to the situation in which the data are analyzed separately. The possibilities of low cost measurement techniques are explored in surveying the levels of nitrogen in the environment. A novel type of modelling of the deposition of nitrogen to natural areas will be used taking into account the characteristics (structure, vegetation type) of the areas.

7.3.4 Planned activities

1. Development, validation and testing of low cost measurement techniques
   Development and validation of a mini lysimeter; an instrument with which the nitrate concentration in percolation water can be measured; development of dry deposition instrumentation.

2. Measurements of nitrogen compounds
   The networks for measurement will be extended with measurements of nitrogen components a) in air and b) in percolation water at sites with a deep groundwater level. The dry deposition estimates will be derived via inference from concentration measurements and modelling.

3. Improved deposition estimates on nature areas
   The atmospheric deposition of nitrogen at the sites will be based on a combination of the measurements in air and model calculations of the deposition process.

4. Statistical analysis of nitrogen data
   The relation between the nitrogen deposition and the nitrate leaching to the upper and deeper groundwater will be evaluated in a statistical way.

5. Analysis of the nitrogen data using deterministic models
   The relation between the nitrogen deposition and the nitrate leaching to the upper and deeper groundwater will be evaluated using soil-vegetation-leaching deterministic models.

6. Derivation of a simplified method
   A simple method will be developed based on the analysis under 4 and 5 that explains the relation between the nitrate concentration in groundwater and the atmospheric deposition, taking into account soil type, vegetation and climatology.

7.3.5 Planned products

Products are:
- Operational minilysimeter
- Low cost deposition equipment
- Monitoring data
- Improved description of deposition estimates
- Simple deterministic model for nitrate leaching
- Several reports and scientific publications

30 The project is related to several monitoring networks in the Netherlands and to DOAS (Differential Optical Absorption Spectronomy).
7.3.6 **Foreseen follow-up**

The improved deposition estimates may lead to other conclusions in the risk analysis of the nitrogen load on nature areas. This is of particular importance to the ministerial department of environment and may lead to new assignments in this field. Data of the networks are analyzed in relation to each other. It is expected that this leads to a further harmonization and optimization of the networks.

7.4 **S/680002 CESAR: Climate and Air Quality Monitoring, Ir. A. Apituley**

7.4.1 **Motivation**

Climate changes, causing sea level rise and change of precipitation patterns, will have important consequences for spatial planning and economy. Large uncertainties are associated with the models and scenarios. Airborne particulate matter (PM) can lead to a wide range of detrimental health effects. More knowledge about the abilities and shortcomings of a variety of PM monitoring is needed. CESAR is the national focal point for collaboration on climate monitoring and atmospheric research. CESAR combines many essential measurements that are needed to reduce uncertainties in our understanding of climate. The potential of the site can be further exploited to use it to bind together the associated observations of climate and air quality parameters.

7.4.2 **Aim of the project**

The aim of the project is to integrate observation strategies for air-quality, climate change and parameters needed to study health related effects on aerosols. Specific aims are:

- Development and exploitation of CESAR for advanced instrumentation for climate monitoring. This will be accomplished through participation in CESAR steering bodies.
- Sustained observations of advanced climate parameters. Advanced techniques will be added to the CESAR Water Vapour, Aerosol and Cloud Lidar for simultaneous temperature measurements.
- Set-up and operation of comprehensive measurements of Particulate Matter at ground level at CESAR.
- Use of the unique possibilities of the CESAR Water Vapour, Aerosol and Cloud Lidar to remotely measure aerosol micro-physical parameters.
- Use of the unique possibilities of the CESAR research station for validating and improving satellite measurements of aerosols and particulate matter.

7.4.3 **Strategic and innovative aspects**

The importance of the comprehensive research station CESAR is widely recognized. Development of the site as a central node in international networks is important. The project will provide gap-filling knowledge on atmospheric profiling to reduce uncertainties in the understanding of climate change. A

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31 The project is related to national and international projects on climate, aerosols/particulate matter and air quality, e.g. EARLINET-ASOS, SatLink, AeroPro, EUSAAR, AQURES (SOR-project) and RAPTES (SOR-project).
Raman lidar will be developed, necessary as a key-instrument. New techniques will be developed, demonstrated and validated.

7.4.4 Planned activities

1. CESAR participation
   RIVM participation in CESAR steering bodies and related gremia is embedded in this project, including an international symposium which will be organized in the Netherlands. New initiatives linking CESAR to similar stations within Europe and other regions, including the US and Asia, are expected and will be supported through this project.

2. CESAR Water Vapour, Aerosol and Cloud Lidar (Caeli)
   The development and operationalisation of an advanced Raman lidar for profiling of water vapour, aerosols and clouds (Caeli). After this, routine measurements will be performed. Data will be disseminated through centralised databases (e.g. CESAR and EARLINET) and used within these projects and in other projects related to CESAR.

3. SuperSite Particulate Matter measurements
   CESAR will be used as a test bed for new monitoring strategies of aerosol parameters. Exchange of information on health related aspects of PM/Aerosols will be established with the appropriate research groups.

4. AeroPro - Raman Lidar determination of the influence of the assumed aerosol vertical profile on aerosol retrievals from space.
   AeroPro (GO2) aims to develop and apply innovative techniques for estimating vertical distributions of aerosol optical and physical characteristics.

5. SatLink - Linking ground based and space borne aerosol/PM measurements
   The SATLINK project (GO2) aims at demonstrating that validated Particulate Matter maps for the Netherlands can be derived from satellite observations. Ground based PM2.5 measurements will be related to satellite-based aerosol measurements.

7.4.5 Planned products

- Time series contributed to various databases of advanced vertical profiles and ground based aerosol parameters.
- Knowledge on the capability of current satellite instruments to observe PM10 and PM2.5 fields over Europe, relevant to the health effects of aerosols.
- Knowledge on the capability of current satellites to observe aerosol optical density and other aerosol parameter fields over Europe, relevant to regional climate change.
- Embedding of CESAR in European climate and air quality monitoring networks.
- Prominent positioning of the Dutch research community, including RIVM, through the organisation of an international meeting on tropospheric profiling.
- Publications in peer-reviewed journals and at national and international conferences.

7.4.6 Foreseen follow-up

Results of this project will be used both inside and outside RIVM. Once the project has been completed, further assignments are foreseen from, the Netherlands Environmental Assessment Agency (MNP), Dutch ministry of
Environment (VROM), the European Union (EU) and the European Space Agency (ESA).