National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Strategic Research RIVM 2011-2014

Project summaries

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Colophon

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This investigation has been performed by order and for the account of DG RIVM, within the framework of Strategic Research RIVM.

Abstract

Strategic research RIVM 2011-2014, project summaries

This report presents the summaries of the project proposals of the Strategic Research Programme (Strategisch Onderzoek RIVM, SOR).

The National Institute for Public Health and the Environment (RIVM) in the Netherlands has a dedicated budget for initiating and carrying out strategic research. Through its Strategic Research Programme (Strategisch Onderzoek RIVM, SOR), the institute is able to anticipate upcoming research questions, to ensure the quality of its scientific expertise and to participate fully in long-term international research networks.

The Strategic Research Programme is set up using four-year programme and budget cycles. The current cycle started in January 2011. The programme comprises of seven strategic research themes, which together cover 79 individual research projects.

Keywords:
Strategic research, innovation, themes, scientific

Rapport in het kort

Strategisch onderzoek RIVM 2011-2014, projectsamenvattingen

Dit rapport bevat de samenvattingen van de projectvoorstellen voor strategisch onderzoek van het RIVM in de periode 2011-2014.

Het RIVM beschikt over een budget voor strategisch onderzoek, het Strategisch Onderzoek RIVM (SOR). Hiermee anticipeert het instituut op toekomstige onderzoeksvragen. Daarnaast versterkt het de wetenschappelijke basis van het RIVM,onder andere door deel te nemen aan internationale wetenschappelijke netwerken.

Voor het SOR wordt elke vier jaar een strategisch onderzoeksprogramma uitgevoerd, waarin telkens nieuwe strategische speerpunten worden gekozen. De huidige cyclus is gestart in januari 2011 met zeven speerpunten.

Trefwoorden:
Strategisch onderzoek, innovatie, speerpunten, wetenschappelijk

Contents

1 Introduction

This report presents the summaries of the project proposals selected for the Strategic Research Programme (Dutch abbreviation SOR) of the National Institute for Public Health and the Environment. The Strategic Research Programme passes through a four-year cycle. The projects presented have been selected for the period 2011-2014.

Aim of the Strategic Research

The aim of the Strategic Research 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, seven strategic themes were formulated:

1. Application of new technologies (ANT).
2. Filling the gap: from knowledge to action (FKA).
3. Healthy ageing (HEA).
4. Healthy and sustainable living environments (HSL).
5. Infectious disease dynamics (IDD).
6. New dimensions on integrated (risk) assessments in public health and environment (IRA).
7. Strategic vaccine research (SVR)

The next seven chapters comprise a description of the seven strategic themes, a project list and the summaries.
The appendix shows a list of all projects.

2 Application of new technologies (ANT)

2.1 Strategic aims

Societal impact
Technological innovation is a key driver of societal progress. The past decades saw rapid developments in information technology and, more recently, in genomics-related technologies and nanotechnologies.
Information technology for one has proven to be a 'breakthrough technology' with wide-ranging effects on society and the economy. In the health arena, many new applications have now been developed, including 'e-health', the use of self-tests and applications of nanotechnologies in consumer products, medical applications, nutrition and diagnostics.

Societal developments such as ageing populations, lower availability of health care workers, zero-tolerance and a simultaneous downsizing process of government are trends that demand higher efficiency and effectiveness in health care. In a society, which often considers technological solutions the panacea for all environmental problems, there can be a supportive role for information technology and other technologies. Parting from this viewpoint, the discovery of a solution for emission problems is only a matter of time: existing methods that now pollute the environment will eventually be replaced by clean techniques. Another advantage of new technologies is the shorter time frame that is necessary to present results in areas of virtual importance, such as the RIVM's calamity tasks. However, in order to enforce such a breakthrough, potential opportunities for technological innovation have to be recognised and realized.

The formulation of integrated health and environmental policies depends on integrated data, resulting in practicable knowledge. Thanks to its independent position, the RIVM has a considerable amount of data at its disposal. However, are these valuable and costly data optimally shared and put to use? There seem to be opportunities for more efficient use. Especially the field of bioinformatics – which heavily depends on information technology – is expected to become a catalyst for more efficient use of data in the field of public health and the environment.

Description and impact in relation to RIVM tasks
The primary focus within this research theme targets the exploration and innovative use of new technologies including bioinformatics. It should be noted that this research theme does not entail the development of new technologies. For example, it entails the implementation of new technological developments within existing work processes, if it increases the quality and timely delivery of results, where possible with lower costs. It also concerns the monitoring and evaluation of developments – supporting the government in its role to safeguard societal interests – in order to take measures when necessary. Naturally, this responsibility demands up-to-date knowledge of the societal impact of technological developments on the citizen, professionals and the health care system.

'Horizontal Scanning' could adequately describe the role of the RIVM in this process. Infused by the global financial crisis, cost reductions will be a primary motive for innovation in the fields of public health and environment. This financial aspect represents an indispensable part of activities within this research theme. However, the main focus of RIVM research on this theme is set to produce a balanced assessment of the significance of technological innovations.

Data collection and processing include the effective use of large quantities of data. As a developing science of growing importance, bioinformatics offers

innovative tools to improve data processing that are also applicable in RIVM activities. For example, internet research for new tools can contribute to the more efficient use of both current and new data.

Whereas investigations into the risks of new technologies are not the primary goal of this research theme, risk monitoring and reporting complement other activities and are valuable by-products of research efforts under this theme. The development of guidelines for use or certifications of new technologies are explicitly excluded from the scope of this research theme.

Focus and future direction of projects
Projects in this research theme focus on assessing the effects of new technology applications in the areas of public health, health care and the environment. Questions that are central in this research theme are:

- What new technologies are already being applied and to what effect?
- Which factors contribute to successful application of new technologies?
- Which new technologies can or should RIVM itself implement to better advise its clients? Would such technologies need to be further developed?
- To which future technologies should RIVM be prepared to respond in order to better execute its tasks?
- How can bioinformatics support the disclosure and processing of large quantities of data?

In order to be well connected to available knowledge, this research theme will require cooperation with other institutes that are active in the field of technology research and implementation, such as TNO and the Rathenau Institute. The specific role of the RIVM should always be the guiding principle for the formulation of research proposals; rather than becoming a bioinformatics specialist the RIVM should primarily gather and apply knowledge that was developed by other institutes.

International connections
Technological innovation is central to many national and international areas. In its 2007 White Paper 'Together for Health: A Strategic Approach for the EU 2008-2013', the European Commission identified supporting dynamic health systems and new technologies like e-health, genomics and biotechnology as a key objective. The European Centre for Disease Prevention and Control (ECDC) listed scientific assessment of current and new methods for disease prevention and control as a priority in its 2008 vision document 'Protecting Health in Europe, Our vision for the future'. And the European Food Safety Authority (EFSA), in its 'Strategic Plan 2009-2013,' named keeping up with science, innovation and new technologies one of its four main challenges.
Many international research programmes offer opportunities for research into the assessment and application of technological innovation.

Keywords
innovation, home care, biomedical technology, biomaterials, personal care, ICT, nanotechnology, screening, e-health, personalized medicine, bioinformatics, calamity functions, sensor, diagnostics

2.2 List ANT

Number	Title	Project leader	Int.
S/210126	Participating in health care IT	Kit Buurman	
S/210136	Using pathogens sequence databases to interpret outbreaks and monitor the national vaccination programme	Marijn van Ballegooijen	
S/270186	Impact of medical technology	Johan Polder	
S/340003	Human stem cell technologies	Aldert Piersma	
S/340004	Application of proteomics-based screening assays	Annemieke de Vries	
S/680020	Monitoring networks of the future	Hester Volten	
S/680025	Modeling of elemental carbon and ultra-fine particles	Eric van der Swaluw	*

Int. = international project cofinanced by SOR-budget

2.3 Summaries

Title:	**Participating in health care IT**
Project number:	**S/210126**
Project leader:	Ir. K. Buurman (Kit) (IF-EMI)
Start:	01-01-2011
End:	31-12-2011
Total SOR-budget:	€ 50,000

Motivation
The application of information technology in health care is booming. Now that most systems for specific health care practitioners have been built, information exchange between health care systems and in chains is being developed.
RIVM has a huge interest in a national health care infrastructure, as a publisher of mostly data-derived knowledge. Most of RIVM's research products are based on datasets that have been gathered nationwide. Yet so far, RIVM has played but a modest (yet significant) role in realizing an infrastructure for health care Information Technology (health care IT). However, RIVM's involvement in the national health care IT Infrastructure is fragmented, and not supported by an explicit vision or strategy.

The national infrastructure will dramatically change the way research datasets are gathered. More and more, the data will be derived from automated health care systems. At the moment, RIVM is not sufficiently involved to be able to induce the infrastructure be adapted to its research needs. Often, by the time RIVM gets involved, the infrastructure and standards are an accomplished fact. If RIVM wants to secure research access to these data, it needs to participate more timely and more intensively in the making of the national health care IT infrastructure.
The National IT Institute for health care in the Netherlands (Nictiz) and RIVM are potentially natural partners for building the health care IT infrastructure. Nictiz has the technical knowledge to build the IT infrastructure, while RIVM possesses the necessary health care process knowledge. The cooperation between the two organizations needs a stimulation, which this SOR-project can provide.

Aim of the project
This SOR-proposal aims to expand RIVM's participation in the national health care IT infrastructure:
- Participating in national infrastructure programmes, meanwhile building a strong network.
- Building up a knowledge base, for participating in and advising current and future RIVM-projects.
- Developing a supporting RIVM-vision and strategy.

Having this vision, network and knowledge 'on board' will make RIVM more eligible for the growing number of external assignments with health care IT aspects.

Strategic and innovative aspects
The innovative nature of this project is not in the invention, but in the application of new technology. The national health care IT infrastructure is taking shape as we speak, including the application of a set of new technologies, amongst others AORTA (Dutch national infrastructure for the exchange of data between health care providers), HL7v3 messaging (non-profit organization

involved in development of international health care interoperability standards) and the National health care Information Hub (LSP).
RIVM needs to take part in realizing the national health care IT infrastructure, to ensure data availability for research and knowledge tasks. Building the national infrastructure requires a major effort: not only technical, but also political, (inter)organizational, administrative, legal and privacy issues need to be addressed. By supplying its knowledge of health care processes, RIVM can help to make the national infrastructure evolve, while making it better usable for RIVM's research and coordination tasks. In doing so, RIVM participates in the nationwide innovation towards the realization of the Electronic health care Records (EPD).

Planned activities

- Continuously: learning by participating. Participating with our partners in the health care IT projects (learning by doing), supplying RIVM health care process knowledge, building up a knowledge base on health care IT standards and technology.
- Analysis: based on workshops with internal and external experts and stakeholders, stakeholder analysis, inventory of current RIVM health care IT projects and interest, analysing these projects on approach and possible improvements, intensifying the network contacts in health care IT (Nictiz and others), writing the analysis chapters of the report.
- Formulating a Vision and Strategy: developing a RIVM health care data & IT vision and strategy, formulating an agenda for the next 3-5 years, writing the vision & strategy chapters of the report.
- Evaluation and consolidation: present successful results within RIVM and possibly other organizations, RIVM Management Approval of the health care IT vision and strategy, evaluating the project, securing the activities as a regular information management task in the IT organization.

Planned products

- A report, containing an analysis, a vision and a proposed strategy.
- A built-up knowledge base.
- An (extended) network.

Foreseen follow-up

Benefits from the project results will be:

- Improvements to a number of 'health care applications' built on the national infrastructure for health care IT, to which RIVM has long-term commitments such as e-diabetes, Spirit (organization providing products for National Health Service) and e-Youth health care (e-JGZ).
- Better access to nationwide research data for many of RIVM's projects, whether they are research, policy evaluation, or screening-based.
- A knowledge base at RIVM on the national IT health care infrastructure, supporting RIVM's growing number of health care projects that need to deal with electronic information exchange.
- A better position for RIVM for acquiring external research assignments with health care IT aspects.

Title:	**Using pathogen sequence databases to interpret outbreaks and monitor the National Vaccination Programme (SEQDAT)**
Project number:	**S/210136**
Project leader:	Dr. W.M. van Ballegooijen (Marijn) (CIb-EPI)
Start:	01-01-2011
End:	31-12-2013
Total SOR-budget:	€ 333,500

Motivation

Genetic sequence information of pathogens sampled from infected cases is becoming increasingly available. As a consequence, the national and global distributions of pathogen strains are known with varying detail through several (inter)national sequence databases. In some cases, this data can be augmented by epidemiological information related to the infected cases. The key question that arises when a number of infections are identified within a short period is whether they are related through transmission, or if they stem from unrelated sources.

The distinction between linked and unlinked cases or outbreaks is crucial for implementing effective control measures to limit further spread. The detection of cases that are related through transmission is important both for monitoring impact of vaccination programmes in the population, and for early intervention in outbreaks. Traditionally, one looks only at the genetic difference between such cases to infer a transmission relationship. But this cannot provide a full answer: while it is easily concluded that cases are not related through transmission when their genetic signature is very different, interpreting genetically similar cases is much more problematic. As an example: when two samples of an indistinguishable sequence are found, this could be seen as evidence of transmission from a common source, but if these samples would be from a sequence that is common in the genetic background, this evidence becomes less substantial. The level of information in the genetic signature may vary between pathogens and along the genome of a single pathogen. Sequence databases can provide insight into this genetic background and are therefore essential in weighing evidence for ongoing transmission.

The objective of our project is to answer the question whether or not infected cases are related through transmission from a common source.

Aim of the project

The aim will be to develop and apply statistical algorithms to analyse sequence databases and newly sampled sequences. The methods will be based on so called Sequential Monte Carlo algorithms (or Particle filtering) and scan statistics. Basically, particle filtering is a techniques used in computer learning. Through iteratively updating information, such algorithms are able to 'learn' characteristics from previously identified outbreaks and apply this to newly sampled sequences. Scan statistics look for clusters in noisy data, such as outbreaks in surveillance time series data.

Strategic and innovative aspects

The project is at the interface of computer science, public health and molecular epidemiology. It addresses the increasing importance of rapidly growing pathogen sequence databases for public health. Developing methods to use this wealth of data to answer relevant public health questions can have international relevance and fits with the core tasks of national public health institutes to

monitor outbreaks, imported infectious disease and vaccination coverage. The project is in line with the ambition of RIVM to host international sequence databases, and collaborate closely with other institutes that host these.

Planned activities

The project is phased into the following three modules.

Method development

- Expertise development, as the methods we aim to use are advanced and we expect any candidate to require time to prepare.
- The core of this module consists of implementing the statistical methods as computer code and to test these on simulated epidemiological data. Results will be published in a peer reviewed journal and presented at an international conference.

Application to norovirus and hepatitis A outbreaks

- Norovirus and hepatitis A sequence data is actively curated and analysed at the RIVM, so that this module builds upon existing and ongoing work in detecting (food related) outbreak clusters in international surveillance data and other settings.

Application to Measles vaccination

- This module will start with orientation on measles vaccination, measles surveillance and measles molecular surveillance. Application of our methods on this data to answer questions surrounding vaccination should result in a peer reviewed publication and conference presentation.

The project will start with an evaluation of what type of implementations are most useful to the RIVM, which activities need to be developed and which are already available in-house. Based on this analysis, the SOR supervisory committee will decide upon continuation of the project.

Planned products

- Three peer reviewed papers.
- A suit of algorithms that can be used to analyse surveillance data, early detection of outbreaks, case attribution and monitoring protection in vaccinated populations.
- Embed the skills and knowledge to apply these tools in the modelling team at CIb so that acquired knowledge is retained after project completion.
- Evaluation of the potential role for these methods in outbreak detection and routine monitoring, both methodologically and in relation to available data and public health questions. We will explore the interest of scientific journals to publish this as a review.
- Memorandum identifying applications and opportunities of these methods for the RIVM.
- Leaflet or letter for the Ministry of Health, Welfare and Sport (VWS) and other external partners to explain the project results in an accessible way.

Foreseen follow-up

Molecular surveillance of infectious disease will increase in importance as molecular methods of analysis become cheaper and more widespread. Consequentially, the historical record of collected sequences will continue to grow, opening up new avenues for applications. We believe our methods for using existing datasets to help interpret outbreaks and monitor vaccination will be of general interest for public health institutes responsible for disease surveillance, vaccination and outbreak containment.

Upon completion of the project we will evaluate our results. This evaluation should include identifying data sources (other than measles vaccination and norovirus and hepatitis A outbreaks) that may contain information relevant for disease control that our methods can divulge. Should our method prove

successful we will aim for follow-up through specific grant applications. This evaluation should also identify data requirements and new opportunities in (molecular) surveillance.

Title:	**Impact of medical technology**
Project number:	**S/270186**
Project leader:	Prof. dr. J.J. Polder (Johan) (V&Z-VTV)
Start:	01-07-2011
End:	31-12-2013
Total SOR-budget:	€ 498,900

Motivation

The introduction and application of new medical technologies is seen as a driving force behind the development of population health as well as the increasing Health Care Expenditures (HCE). Other factors comprise epidemiological transitions and the ageing of the population. Regarding the latter, new evidence from health economic literature has demonstrated that population ageing is a 'red herring' in the explanation of the observed growth in HCE over the years, as it erroneously diverts the attention from other factors that might influence HCE, such as medical technology.

However, little is known about the extent to which medical technology influences HCE and population health, mainly because measures to quantify growth and impact of technology are limited.

Facing ageing populations and increasing health care needs, it is important to know whether or not advances in medical technology can contribute in explaining the rise in HCE and explain changes in population health. In this project a first attempt will be undertaken to unravel the influence of medical technology on HCE and population health.

Aim of the project

The aim of the project is to unravel the influence of advances in medical technology on HCE and population health. Three study objectives are distinguished:

- Charting the progress of medical technology based on evidence from the Dutch situation. This comprises three goals:
  - Defining the scope of medical technology and classifying types of technology, based on the specific function within health care (e.g. prevention, alleviation of disease) and the disease they are targeted at.
  - Describing exemplary cases of medical technology advances. Given available sources of data, cases of medical technology advances which are considered as exemplary for each classification of medical technology (e.g., drugs, treatments, and assistive devices) are selected.
  - Deriving quantitative measures for these exemplary cases to describe the duration of the innovation and diffusion phases.
- Quantifying the effect of advances in medical technology on HCE by applying the measures as derived from.
- Quantifying the effect of advances in medical technology on population health parameters by applying the measures as derived from.

Strategic and innovative aspects
Quantifying effects of advances in medical technology in terms of HCE and health parameters at the population level over a longer period of time is unprecedented in the Netherlands and positions RIVM into a significant role in the field of health and HCE projections. Unravelling the effect of advances in medical technology on HCE and population health calls for intensive cooperation at the interface of medical technology, medical practice, health economics, epidemiology, and demography.
A primary innovative aspect of the project at hand is the development of a methodology to quantify the advances of medical technology by developing two measures of growth, based on the concept of the intergeneration time and the level of diffusion. Linking these two measures of medical technology advances to the growth in HCE and parameters of population health is another innovative aspect.

Planned activities
- Defining medical technology advances.
- Finding exemplary cases for medical technology advances.
- Apply for data, obtaining and preparing the data to quantify these exemplary cases.
- At least one publication in refereed journal on medical technology advances.

Go/no-go decision

- Data preparation, preliminary analyses.

Go/no-go decision

- Quantifying innovation and diffusion effects on health care expenditures for each exemplary case.
- Quantifying innovation and diffusion effects on population health parameters for each exemplary case.
- At least two publications in refereed journal, one for each relationship (population health and health care expenditures).

Planned products
The main foreseen products are at least four publications in international peer reviewed journals:
- One paper will describe innovation and diffusion phases of the selected exemplary cases.
- Two papers will deal with the relationship between medical technology advances and population health, and health care expenditures, respectively.
- The final paper will give an overview of all results, and present the implications for research on health and health care expenditures.

Additionally, the publications will yield input for three RIVM products that are targeted at policymakers:
- The 2014 Public Health Forecasting Report.
- The 2014 Cost of Illness study.
- The Dutch Health Care Performance Report. Subject to the abstraction level of the results, additional RIVM products might utilize project outcomes, such as the Chronic Disease Model.

Finally, several memoranda will be made, specifically tailored at communication with our (potential) knowledge users. A workshop will be given to disseminate the knowledge that has been acquired within this project.

Foreseen follow-up
The results of this project can be used in scenario studies of future health and health expenditure. We foresee that this project could lead to future assignments from several Dutch ministries and government agencies. Additionally, this project might contribute to health care expenditure methodology in other countries. This might lead to cooperation with members of the Technological Change in Health Care Research Network (TECH group), Eurostat (statistical office of the European Union), and the Organisation for Economic Cooperation and Development (OECD).
The project will also provide incentives for future research. Particularly, further research on the determinants of innovation and diffusion of technologies is foreseen.

Title:	**Human stem cell technologies**
Project number:	**S/340003**
Project leader:	Prof. dr. A.H. Piersma (Aldert) (VGC-GBO)
Start:	01-01-2011
End:	31-12-2012
Total SOR-budget:	€ 331,900

Motivation
Human stem cell technologies represent an area of rapid current innovations in a large and growing variety of applications in medical technology and animal free alternative tests in toxicology.
It is anticipated that many applications will reach the stage of implementation in the coming decade, which will raise questions about e.g. the efficacy, safety and ethical aspects of medical applications, and the predictability and applicability of stem cell based animal-free toxicity tests in toxicological hazard assessment. In the near future, the Dutch government will be confronted with the implementation of these technologies and will have to regulate their use in clinical and toxicological practice. RIVM anticipates these developments and is building knowledge and expertise in stem cell technologies in order to enhance its expert advisory role for the Dutch government in this area.
This project will be the first to introduce human embryonic stem cell models at RIVM. One of the critical aspects of chemical risk assessment is interspecies extrapolation. Human risk is currently estimated almost exclusively on the basis of animal studies. The application of human embryonic stem cell lines could provide two advantages in this context. First, it may reduce animal use in safety testing, and second, it makes use of material from the target species, mankind, excluding the need for interspecies extrapolation. Scientific developments in alternative testing are moving towards using human cells wherever possible. Both the Dutch ASAT initiative (Assuring Safety without Animal Testing) and the US-NAS (United States National Academy of Sciences) report 'Toxicity testing in the 21st century' have embraced these developments. It is therefore timely and necessary to expand our expertise to human embryonic stem cell models. We will make use of commercially available existing cell lines, that are approved for research use under Dutch and European legislation.

Aim of the project
Human stem cell models: introduction and development of animal-free alternative toxicity assays based on human embryonic stem cell lines, and their implementation in the testing strategy for chemical safety assessment.

Specific objectives:
- Stem cell differentiation: introduce and develop culture techniques for human embryonic stem cell differentiation. Specific differentiation pathways that will be studied are: cardiac muscle, neurons, bone, liver.
- Alternative test systems: apply these human embryonic stem cell differentiation models to generate alternative tests for toxicity testing.
- Toxicity testing strategies: survey the application and implementation of novel stem cell based assays in testing strategies for chemical hazard identification with policymakers.

Strategic and innovative aspects
Human stem cell technologies provide a wide variety of innovative scientific developments which are anticipated to find many applications in personal health care and chemical risk assessment in the coming decade. These developments come with important and as yet ill addressed issues related to efficacy, safety, quality of life, societal impact and ethical acceptability. As the prime advisor for government on new developments in public health, the independent knowledge centre RIVM must be prepared to take its responsibility and enhance its profile as the principal national expert institute in this diverse and complex area of expertise. In rapidly developing areas such as stem cell technologies, knowledge equals expertise. It is therefore of high strategic importance that RIVM introduces human stem cell cultures and contributes to the forefront of scientific developments. This project focuses on their application in models for chemical safety assessment, which is a globally recognized core function of RIVM in the Netherlands and abroad. In addition, it allows the subsequent initiation of novel regular projects from our counterparts such as at the Ministry of Health, Welfare and Sport.

Planned activities
- Stem cell differentiation.
- Alternative test systems.
- Toxicity testing strategies.

RIVM will invest in technological developments and monitor applications in toxicological testing to refine chemical and pharmaceutical risk assessment and estimate reductions experimental animal use in testing strategies. RIVM will expand its own technological knowledge by adding human stem cell differentiation culture technology as a basis for RIVM expert advice on the subject.

Planned products
- Scientific publications: New cell culture models for the study of chemical toxicity based on human embryonic stem cell lines (at least two publications on two different differentiation lineages). Evaluation of predictability of cell culture models with a limited group of chemicals (at least two publications on different differentiation lineages).
- RIVM final report: Overview of the state of the art of human stem cell technologies as to their development and implementation in chemical safety assessment.

Foreseen follow-up
RIVM will profit from the scientific output in two ways:

- First, it will signify and consolidate its leading role in embryonic stem cell derived animal-free alternative assays for toxicity testing and their application in innovative alternative testing strategies for chemical safety assessment. This work will be performed in close collaboration with other existing projects aimed at developing new cell culture models, animal-free toxicity tests and alternative testing strategies, generating critically important synergy advantageous for each of the contributing projects.
- Second, this work will position RIVM as the lead advisor for government in the area of stem cell technologies, as to their applications in toxicological hazard assessment. This activity is aimed at providing continuity of RIVM's status as an expertise centre in the design of alternatives to animal testing, and the development of innovative methods of hazard and risk assessment strategies.

The Dutch Ministry of Health, Welfare and Sport will profit from the expertise emanating from this project. In RIVM they do find their natural partner as their scientific advisory institute for public health. Moreover, this project will establish RIVM as their primary advisor in matters related to the toxicological application of stem cell technologies. A series of regular projects on a variety of these aspects that are relevant for public health policy can be anticipated.

The scientific and regulatory community beyond the Netherlands will also profit from this investment. EU and other international scientific projects, and technical and regulatory committees in bodies such as in EU and OECD (Organisation for Economic Cooperation and Development) will continue to be able to take RIVM on board as a desired partner with specific expertise relevant to the important and timely subjects of stem cell technologies and their implications, reduction of animal use in safety evaluation, and improvement of chemical hazard and risk assessment.

Title:	**Application of proteomics-based screening assays**
Project number:	**S/340004**
Project leader:	Dr. A. de Vries (Annemieke) (VGC-GBO)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 1,373,500

Motivation
The RIVM is leading in the detection and monitoring of infectious outbreaks and emerging infectious diseases, as recently illustrated by new Influenza A, Q fever, and Lyme disease, which are all zoonotic by nature. Furthermore, the RIVM coordinates several large-scale population screening programmes, among which the Down Syndrome and breast cancer screening. It is anticipated that the number of population-screening programmes, as well as infectious outbreaks will increase in the near future. In addition, (inter)national technological progress in the field of screening is evolving fast and will affect the current screening programmes. This project aims at exploring the applicability of a major new development in screening of zoonotic infections and human diseases: detection assays based on innovative proteomics techniques.

Aim of the project
We will explore the use of and apply operational proteomics techniques in several relevant screening assays for detection of emerging zoonoses, breast cancer and prenatal trisomy syndromes.

Strategic and innovative aspects
Proteomics is a novel technology whose applicability is (inter)nationally rapidly progressing. To sensitively detect various conditions and/or diseases in serum applying proteomics is innovative and the exploration of this is currently broadly initiated in several research and screening fields. Innovative proteomics techniques are expected to play an important role in developing future and/or improving current population screening tests, including in areas of virtual importance such as the RIVM's calamity tasks. Given the important role the RIVM plays in the Netherlands in coordinating several population screening programmes as well as in monitoring infectious outbreaks, it will be highly important to monitor and evaluate new developments in screening applications in all these areas.
We will explore the use of proteomics assays in all these emerging screening fields, rather than focus on one, since applications will benefit from progress and experiences in another. To explore this, we will organize a RIVM colloquium unrolling the experimental platform and knowledge, to allow other RIVM researchers access.
Finally, focus on application of new technologies for early disease detection and broad population screening, as proposed here, is important for RIVM, since in academic and industry settings focus has been mainly on clinical application of biomarkers. RIVM should be prepared to these (future) technologies in order to continue executing its screening tasks properly. In this project we will acquire and provide screening coordinating centres at RIVM with early alerts of these new developments through our research activities and associated collaborations.

Planned activities
- Select/identify through bioinformatics approaches potential biomarkers for the conditions to be screened for.
- Design/compose Antigen and Antibody arrays.
- Validation phase.
- Implementation phase.

Planned products
- RIVM Symposium/colloquium showing researchers at broader RIVM the possibilities of applying proteomics techniques in different areas RIVM is involved in. Special attention will be given to the experimental proteomics platform set up by us that will be available to other research lines and RIVM researchers.
- Shared peer reviewed scientific publications, including PhD theses, between RIVM departments and collaborators.
- Two PhD theses.
- Ten to twelve scientific publications.

Foreseen follow-up
Expected benefits:
- Communication and exchange of research experience between experimental Strategic Research RIVM (SOR)- researchers and programme coordinators in screening areas RIVM is involved in will strengthen knowledge transfer between research and coordinating centres at RIVM. 'Bridging the gap' between research and practice will allow RIVM to better monitor new developments in screening tasks.

- It is a conscious choice to integrate different applications of new proteomics screening assays within this one project to enable intense collaboration between centres and divisions, including exchanging personnel.
  Extended collaboration between different RIVM departments sharing the technological proteomics platform will benefit technological innovation at all departments, favouring future applications.
- Strategic alliances with Dutch universities and other knowledge institutes allow knowledge exchange and makes academic progress applicable for RIVM screening tasks.

New assignments outside RIVM:
Involvement in novel screening methods potentially applicable in screening programmes will likely open new grant application possibilities and commissions from the Ministry of Health, Welfare and Sport in the future. For emerging zoonoses, new assignments will be expected.

Title:	**Monitoring networks of the future (MONET)**
Project number:	**S/680020**
Project leader:	Dr. H. Volten (Hester) (MEV/CMM)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 904,800

Motivation
Operational monitoring networks are cornerstones of environmental policy. They provide a continuous diagnosis of the state of the environment, and are an essential tool in monitoring the effectiveness of environmental policy. To ensure homogeneous datasets of high quality, monitoring networks use stable instrumentation and fixed procedures. Still, it is essential to be able to respond to novel developments in measurement techniques and methods with which air pollution issues can be monitored. This project aims to study a number of these new developments expected to find their way into the Dutch National Air Quality Monitoring Network in the near future.

- In work package 1, the issue of the excess deposition of nitrogen on nature areas is considered.
- Work package 2 deals with the air quality issue particulate matter (PM), of which the loads in the Netherlands frequently exceed European Union standards. Both are persistent environmental issues in the Netherlands.
- Work Package 3 addresses integration of ground-based measurements, satellite data and modelling efforts. This is expected to become more and more important for air quality monitoring networks, and will encompass the issues from the other two work packages.

These issues are strongly related. For example, in work package 2 we aim at the identification of particulate matter in the form of ammonium salts that, like ammonia, add to the problem of nitrogen deposition addressed in work package 1. In addition, both particulate matter and ammonia are measured from space by satellite instruments. The intertwining of the three work packages is also reflected in the multiple roles of our external partners.

Aim of the project
This project aims to improve the National Air Quality Monitoring Network by using novel techniques and methods in three key environmental issues:

- Ammonia deposition will be measured with a recently developed state of the art but inexpensive instrument.

- Particulate matter will be characterized in real time and at low cost, especially in relation to its source, as is relevant for health effect studies.
- The integration of satellite and ground based data (including this newly gained data) on the one hand and modelling activities on the other will be evaluated, and its implications for the monitoring network will be assessed.

The specific objectives of this project are:

- Testing of a new ammonia deposition instrument.
- Testing SPEX as ground-based instrument, and guiding its development for use in a monitoring network.
- Evaluating the implications of current developments in modelling and data assimilation on the set-up of monitoring networks.
- To define an optimal balance between satellite and ground-based monitoring and modelling of air quality.

Strategic and innovative aspects

Currently, in the Netherlands, RIVM has a leading position in the research field of ammonia in the environment. The development and deployment of an ammonia deposition measuring instrument is essential in obtaining reliable deposition data that is needed for a good assessment of the nitrogen deposition. With this new data, policymakers on nature and nitrogen deposition can be better advised. By taking part in the testing of the ground-based SPEX instrument for measurements of particulate matter, RIVM ensures a position from which to influence its development. In this way, RIVM directs the course of the final stage of the development, so that the instrument is well suited for the needs of air quality monitoring networks in this critical field. Through the Strategic Research RIVM projects SmogProg and AQURES (Air quality and remote sensing), RIVM placed itself in a prominent position in the integration of measurements and modelling in Europe. This proposal seeks to consolidate and capitalize on this position.

The development of an economical, operational instrument to measure ammonia deposition that is easily deployed in a network is highly innovative. Likewise, the SPEX instrument represents a great improvement over the existing methods that are currently employed in monitoring networks to measure particulate matter properties. Integrating air quality modelling and air quality measurements, both from satellites and from the ground, on a European scale is still in its early stages. This field as a whole is highly innovative.

Planned activities

Work package 1: ammonia deposition.

- In the first year, two instruments to measure ammonia concentrations and an off-the-shelf sonic anemometer will be combined to form a deposition instrument.
- Go/no-go decision.
- In the second year, an international comparison campaign will be organized. This will be done in close collaboration with Agroscope Research Centre, Switzerland.
- In the third year, with a possible extension into the fourth year, a start will be made with routine measurements.
- In the third and fourth year, a study will be made to see if the deposition can also be retrieved using the Eddy correlation technique.

Work package 2: particulate matter.

- In the first half year, we will commission the construction of a prototype ground-based SPEX instrument. In the second half year test measurements will be performed with this SPEX.
- Go/no-go decision.

- In the second and third years, the instrument will be operated at one or more sites, where particulate matter is collected on filters and chemically analysed.

Work package 3: assimilation of measurements into models.

- In the first two years of the project, the development of data assimilation will be finalized by our Dutch SmogProg project partners, and by our European partners.
- Go/no-go decision.
- Starting in the second year, but mainly in the third and fourth years of the project, a study will be conducted to assess the impact of new monitoring information (satellites, real time ground-based data) and new techniques (assimilation) on the assessment and forecast of air quality in Europe, especially focusing on summer smog.

Planned products

- The project will deliver several instruments.
- The project will deliver publications in peer reviewed journals.
- Publications on the implications for the monitoring network of the assimilation of satellite and ground-based measurements and modelling, for different components (such as particulate matter, nitrogen dioxide, and ozone).

Foreseen follow-up

Results of this project will be used both inside and outside the RIVM. The Dutch government will benefit from a more reliable assessment of abatement policies to reduce the nitrogen load in the environment by improved modelling of the nitrogen cycle. The ammonia deposition instrument will also be used by our project partner Agroscope Research Station. The general public will benefit through the availability of online and real time measurements of the load of particulate matter, classified to type. SPEX is candidate to fly on air quality satellite missions; the work done in this project will guide its development.

Title:	**Modeling of elemental carbon and ultra-fine particles**
Project number:	**S/680025**
Project leader:	Swaluw, dhr. E. van der (Eric) (MEV/ CMM)
Start:	01-01-2012
End:	31-12-2015
Total SOR-budget:	€ 90.000

Motivation

There is a general concern that traditional air quality indicators like PM10 and PM2.5 do not accurately capture the health-relevant exposure of the population. The rationale behind this concern is that PM consists of a range of particle types of various sizes and compositions, and some particles are more suspect of adverse health effects than others. Among the most suspect are ultra-fine particles (UFP: particles with a diameter less than 100nm or PM0.1) and combustion derived carbonaceous particles soot or elemental carbon (EC). Maps of UFP and EC emissions and concentrations for the Northwest Europe (NWE) territory are currently lacking. Equally important is getting insight in the relative importance of local versus regional or trans-national sources of EC and UFP. Finally, the effect of policy measures taken for the reduction of PM levels on the concentration levels of EC and UFP have to be evaluated.

Aim of the project

The aim of this proposal is:

- To construct regional-scale maps of UFP, EC and PM10 concentrations in Northwest Europe.
- High-resolution concentration maps will be constructed for a number of densely populated cities in Northwest Europe. The maps will be constructed for current concentrations as well as for the reduced levels as a result of policy measures taken for the reduction of PM.
- Calculating concentrations, using a combination of both regional and local city atmospheric transport models.
- Provide an indication for the impact of policy measures on the direct health-relevant exposure of the population.

PM10 concentration maps are included in order to have a reference for the EC and UFP concentration maps and to connect to current EU Air quality legislation.

Strategic and innovative aspects

- This is an emerging scientific issue and of which the results have large policy implications.
- The SOR- project will serve as the co-financing of a work package in the EU Interreg Joaquin.
- This work package will be coordinated by RIVM, which is an opportunity for RIVM to have a leading role in an international project with national and international partners like VMM, ECN, VITO and TNO. More specifically RIVM is interested to lead this action since this enables a principle role in the selection measures to be evaluated (in line with Dutch policy priorities) and in the selection of models.
- The connection with TNO is important because of their access to emission data, the modeling expertise and their role in FP7 projects (TRANSFORM).
- Connection with ECN is important because of their access to measurement data and expertise.
- Connection to the Belgium partners is important because of their modeling expertise.

This project can be an excellent catalyst to (re)join Dutch and Belgium model activities resulting both in comparability of cross border results and efficient use of resources.

Long term profit for RIVM: Assesment of the exposure of the population and the effect of measures is particularly important for RIVM. For example in the monitoring of the "Nationaal Samenwerkingsprogramma Luchtkwaliteit" (NSL). The current system might harm RIVMs reputation as Environment and Public Health Institute. RIVM's role in the NSL, and the access to the corresponding (traffic etc.) authorized data base, provides necessary input data.

Planned activities

Activities:

- Coordination of the project
- Combining emission data on preferred scale/grid
- Definition of scenarios
- Emission input files for scenarios
- Model adaption and test runs
- Calculation model runs (incl. scenarios)
- Local model runs UK
- Synthesis model results and validation
- Reporting

Planned products

- Maps of the distribution of emerging health relevant air pollution parameters (EC & UFP) over the NWE territory;

- Scenarios to assess the transnational effects of large-scale measures like speed limits, a local ban on old cars, certified wood stoves etc.;
- At least one peer reviewed paper with JOAQUIN partners presenting the above mentioned maps;
- The JOAQUIN report;
- Part of the results will be presented on the JOAQUIN website.

Foreseen follow-up

In literature UFP and especially EC are more and more considered to be at least as relevant for health effects as PM. Therefore the long-term profit for RIVM is that the project will provide concentration levels of EC and UFP which enable the assessment of the exposure of the population and the effects of measures. This is especially important for the monitoring of the "Nationaal Samenwerkingrprogramma Luchtkwaliteit" (NSL).

3 Filling the gap: from knowledge to action (FKA)

3.1 Strategic aims

Societal impact
Why do sunbathers still flock to the beach even though it is known that such behaviour will spark many additional skin cancer cases? Why do millions still smoke? How effective are measures to prevent infectious diseases really? Why is the daily intake of healthy nutrition not self-evident?
All of these questions add up to one major question for RIVM and its clients: how can we make more effective use of the knowledge we have collected in our database?
Very often, consumer behaviour does not follow current health expertise. Off course the sole distribution of health and risk related information is not sufficient to effectively influence the behaviour of policymakers, professionals and citizens. These groups are simultaneously guided by other motives, such as skills, motivation and values. Through better health education and promotion, much is yet to be gained that could increase the sustainability of our health (care) systems.

Description and impact in relation to RIVM tasks
Knowledge is at the core of RIVM's work and mission. Whether we do research, provide advice to policymakers or perform other duties such as the direction of major public health programmes, we strongly depend on knowledge. The RIVM is actively involved in all phases of the knowledge chain: development, integration and distribution. Moreover, in a number of research fields there is a growing tendency to shift the emphasis from data collection and research towards direct policy advice and towards execution of programme direction. In fact, whereas universities are primarily charged to carry out basic research, RIVM's niche activities focus on the key concepts of integration and dissemination of the full body of current knowledge.

The successful implementation of knowledge demands a thorough understanding of the other factors that are not knowledge-related but strongly influence human behaviour. For example, the risk perception of target groups can differ considerably from the risk calculations of RIVM experts. Therefore, research about the causes of such behaviour and about respective interventions is of essential importance.

The rapid developments in communication – resulting in more and more citizens to use internet resources such as Twitter and Hyves – require another approach than 20 years ago. This also concerns professionals that perform research through Google and are connected in platforms like Linkedin. These new means of communication and sources of information strongly influence the quantity and speed of available information. In order to stay connected, the RIVM has to anticipate communication through these channels.

Focus and future direction of projects
The final objective of this theme is to acquire understanding how knowledge about public health and the environment is applied by policymakers, professionals and citizens. Subsequently, the testing of new methods and tools for knowledge transfer and implementation into practice is included in this research theme.

More profound transfer of knowledge could be achieved by clearly mapping the users and by inviting target groups to participate in the realisation of policy and research. In this context, small scale pilot projects could enhance the successful implementation of research and help us benefit from the experiences.

Consequently, emphasis should be placed on evaluation of implementation processes: why do some implementation efforts not advance successfully?

Projects within this research theme will require expertise that has not traditionally been available within RIVM, such as social sciences, communication sciences and bio-informatics. RIVM should not aspire to develop expertise in these fields by itself. However, researchers should become knowledgeable enough to be serious counterparts to external partners and to build up capacities to translate external knowledge into RIVM-specific tasks. Within and outside the Netherlands, other expert organizations actively operate in related fields to implement and communicate knowledge. Examples of such partners in the field of public health are ZonMw (Netherlands organisation for health research and development) and universities. Other knowledge partners can be found in the professional networks of community health centres (GGD) and screening organizations.

Throughout this research theme, the concept of 'collaborative development' will be applied. Participation in relevant networks will enhance the overview of knowledge needs of different parties and increase the collection of external knowledge.

International connections
Implementation and communication are highly relevant to international bodies such as the World Health Organization and the EU. At this point, research in this area has not explicitly earned prominent places in their strategic agendas. However, most international research projects include budgets for implementation and communication.
The EU's 7th Framework Programme (FP7) lists 'Enhanced health promotion and disease prevention' as a specific subject, and future Work Programmes may contain calls for proposals in this area. Calls may also be published based on the 'responding to EU policy needs' action.
The EU's 'Second programme of Community action in the field of health (2008 to 2013)', under the topic 'improving healthy lifestyles' mentions the objectives 'improvement of communication skills of health workers' and 'exchange of best practices in the field of obesity' as two of its three objectives.

Keywords
knowledge, effectiveness, risk perception, communication, interactive websites, implementations, outside world, behavioural changes, evaluation, collaborative development, direction of programmes, knowledge transfer, target group participation, influencing behaviour, knowledge management, societal impact

3.2 List FKA

Number	Title	Project leader	Int.
S/205006	ePublic health: fresh approaches to infectious disease control	Desireé Beaujean	
V/205124/01	Communication with vaccine resistant groups in outbreak situations	Jim van Steenbergen	*
S/210086	Monitoring acceptance national immunization programme	Hester de Melker	
S/260206	Health literacy put into practice	Ellen Uiters	
S/260216	Factors influencing willingness to participate in preventive interventions: discrete choice experiments	Ardine de Wit	
S/260286	Combining resources in health care: How can we prepare our human resources to exploit our technological resources?	Mattijs Lambooij	
S/270196	Evidence to inform policymaking in public health	Matthijs van den Berg	
S/270206	Improving knowledge utilization	Hans van Oers	
S/270246	CBIs childhood obesity	Marieke Verschuuren	*

Int. = international project cofinanced by SOR-budget

3.3 Summaries

Title:	**ePublic health: fresh approaches to infectious diseases control**
Project number:	**S/205006**
Project leader:	Mw. drs. ing. D.J.M.A. Beaujean (Desireé) (CIb-LCI)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 436,000

Motivation
Control of infectious diseases, especially during large-scale epidemics or incidental high risk outbreaks, increasingly suffers from deficient compliance with preventive measurements or guidelines of both professionals and general audience. Examples are the no-show rate among the general audience after receiving a personal appeal to obtain an influenza or HPV-vaccination, or similar low adherence among health care workers with preventive measures such as wearing protective gear (like masks, gowns and protection glasses) during professional care for potentially infectious patients, low influenza vaccination or vaccin uptake among health care workers (to protect their patients for hepatitis B or influenza). This poses a threat to public health in the short term.

The RIVM Centre for Infectious Disease Control (CIb) has an executive and coordinating task in the national prevention and control of a wide range of infectious diseases manifesting themselves in incidental outbreaks of mixed origin, scale and risk level, as well as various epidemics. This is one of RIVM's most important and most visible statutory public assignments.

We know that current approaches to prevent risk behaviour are expensive, tired and hardly effective. Fresh approaches are needed. eHealth marketing concerns public health practice. It draws from traditional marketing theories and principles, and adds evidence-based strategies to prevention, communication, health promotion and health protection on a wide range of topics. eHealth marketing typically uses emerging technologies and 'digital media' to improve the impact of health marketing and communication. Web-based and mobile technologies offer tools that are cheap, ubiquitous, interactive, real-time, many-to-many and participative in nature. They can be put to action for CIb (and, indeed all RIVM's) objectives to make content, tools and services available when, where and how users want them.

Aim of the project
The aim of the project is to design, operate and evaluate a limited number of social media tools according to a participatory health care design approach in order to increase adherence to preventive measures and guidelines in infection management in three areas; Pediculus humanus infestation, scabies infestation and a new infectious disease outbreak. Both a professional and a general audience are targeted. The project seeks to establish the value of social media in addition to current media use in public health determining if eHealth marketing can:

- Increase the impact of RIVM's products and programmes.
- Support professionals in improving the health impact of their interventions and adherence to Guidelines.
- Increase adherence with preventive measures by the general public.

The ultimate vision is that people in the Netherlands may live longer, healthier and safer as a result of continuing experiences with interactive, electronic health information and interventions for RIVM and related institutions.

Strategic and innovative aspects
This proposal explores innovative practices in social marketing in order to value their use for RIVM interests i.c. disease control and prevention in de medium term. It responds, among others, to a recent advisory report of the Council on Public Health and Health Care to strategically determine if social media can be put to use in public health. It puts existing knowledge and practices into action.

Due to the novel nature of social media this is an explorative, pioneering study that aims to deliver applicable results. It demonstrates to stakeholders that RIVM responds to cutting-edge developments in health information science to be ready for her future assignments. Outcomes should be applicable not only for infestation and infectious disease control but also for other public health issues and avoidable illnesses. Therefore the outcomes will be integrated in the RIVM-wide communications plan.

Planned activities
The present proposal selects three eHealth marketing tools ((micro-)blogs, social networks, pod casts, mobile applications, RSS feeds) with regard to three distinct infections/infestations/public health threats.
Planned activities are
- Assessment of current RIVM approaches.
- Reviewing of new media use for infection control.
- Participatory design of three social media tools.
- Knowledge into action for prevention and control, health and risk communication.
- Evaluation.
- Modelling scenarios.

Planned products
- Specific model for development and application of mobile and web-based media for infection prevention and control.
- Generic model for development and application of mobile and web-based media interventions for safe, effective and efficient health and risk communication.
- Scientific evaluation tool to measure and monitor the effects of new media interventions in public health.
- Five peer reviewed articles.

Foreseen follow-up
Outcomes will enhance RIVM's statutory assignments in the short term. Outcomes should facilitate health promotion and behavioural change among general and professional target groups, improve health care, improve adherence to public and professional guidelines, reduce health disparities and enhance health care outcomes.

Title:	**Communication with vaccine resistant groups in outbreak situations**
Project number:	**V/205124/01**
Project leader:	Steenbergen, dhr. J.E. van (Jim) (Cib/ LCI)
Start:	01-01-2012
End:	31-12-2013
Total SOR-budget:	€ 104.300

Motivation

Anti-vaccine groups have gained prominence in Western countries in the past years. Such groups might have a religious, ethnic, philosophical or other background. Some of these groups gain a prominent media standing (e.g. on the internet) and can exert considerable influence on the public's decision making process regarding vaccination. It is important to understand the background of these groups and the content of and motivation behind their arguments. These need to be addressed adequately when introducing large-scale public measures such as vaccination and antiviral therapy. To our knowledge, such analysis of these groups does not exist.

More in detail: All vaccines inherently have side effects, and never fully protect all vaccinees. The optimal strategy for an individual in a population to get a minimum of side effects, with a maximum of protection, is not to go for vaccination and to ensure that all your contacts are fully vaccinated. This is a universal dilemma for all human beings in a population. The majority nevertheless (still) follow the governmental advice for vaccination, accepting the individual risk of side effects or other adverse events, and avoiding the risk of not being fully protected.
There is a broad range of motives why people, resistant or critical towards vaccination, organise in groups, from religious and ideological motives to philosophical or purely emotional. Some of the (better organized) groups have a considerable voice in the media, both traditional and digital, influencing the public's opinion.
Most responsible health agencies are quite aware of the composition, ideology and communication means of the most important groups in their respective country, but this information is not available in the open scientific literature. It is unknown how these groups influence societies' attitude towards vaccination, how they deal with the universal dilemma of balancing benefits and adverse events of vaccination. Lastly, responsible health agencies communicate with media, and media use the paradigm to always give room for persons or groups with opposite opinions.
Presenting the total spectrum of groups will enable responsible health agencies to identify specific critical groups and model their communication strategy for optimal understanding of risks and benefits for all people in society, including those with critical opinions.

Aim of the project

A full map will be created of critical and resistant groups in minimally three countries, preferably each country representing the earlier identified different public health systems in the EU.
A systematic literature search will be conducted, including grey literature and internet analysis, bringing together all written and digitally available information on critical and resistant groups.
An analysis will be made of the groups' cultural beliefs in dealing with the universal dilemma of balancing benefits and adverse events of vaccination.

The impact of the most important groups on societies' attitude towards vaccination will be quantitatively assessed in a media analysis by MediaTenor. With the Strategic and Social Marketing group of Prof Jeff French we will develop strategies for the responsible health agencies to communicate with the vaccine resistant groups. If we can present the total spectrum of groups, responsible health agencies can identify and promote certain specific critical groups that can be considered as being "moderately" critical and theoretically "sound", for media to act as groups with opposite opinion.

Strategic and innovative aspects

Up to today, responsible health agencies have not actively sought communication with vaccine resistant groups. Effective communication starts with understanding the cultural beliefs of the respective groups. We will describe and present the cultural beliefs and attitudes of the critical groups with strongest societal influence: how do they deal with the universal dilemma of balancing benefits and adverse events of vaccination, how and where do they obtain, process, weigh and present (scientific) information.
Innovation lies in the multidisciplinary approach where we integrate technical information from media analysis, social information on cultural cognition with communication techniques of social marketing. This multidisciplinary approach is new to the EU and the RIVM. The RIVM can benefit from the experience and findings of this project as these will probably be applicable to other public health intervention fields as well.

Planned activities

- October – December 2011 Administrative and logistic preparation
- January – July 2012: scientific and content preparation
  - Development of theoretical framework; for describing the vaccine resistant groups
  - Identifying three countries to participate in the study
  - International meeting bringing together experts and participating countries to identify gaps in knowledge on the vaccine resistant groups in the selected countries
  - Inventory of the complete spectrum of vaccine resistant groups in three EU countries by literature search, internet search, bringing together written and digital information on vaccine resistant groups.
- April – July 2012: Fieldwork media analysis (Media Tenor)
- August – September 2012: analysis and reporting
- December 2012 - January 2013: International expert meeting at RIVM discussing findings and planning for development of communication strategies (Strategic Social Marketing)
- January - August 2013: developing communication plan for Public Health Authorities (How to deal with vaccine resistant groups in outbreak situations).
- August - December 2013: developing an internet based road map for Public Health Authorities in the EU to communicate with vaccine resistant groups in outbreak situations.

Planned products

- Report consisting of a written complete overview of the spectrum of vaccine resistant groups in three EU countries, partly based on the theoretical framework
- Topic list for focus groups and questionnaire for in depth interviews.
- Report on the activities and social impact of vaccine resistant groups in the written and digital media (Media Tenor)
- Report on beliefs of vaccine resistant groups in dealing with the universal dilemma of balancing benefits and adverse events of vaccination.

- December 2012 - January 2013: International expert meeting at RIVM discussing findings and planning for development of communication strategies (Strategic Social Marketing)
- August 2013: Communication advice for Public Health Authorities of three EU countries how to communicate with vaccine resistant groups in outbreak situations (Strategic and Social Marketing, Prof. Jeff French).
- December 2013: Guidance report (road map) for EU member states how to inventories vaccine resistant groups and for Public Health Authorities in the EU how to communicate with vaccine resistant groups in outbreak situations

Foreseen follow-up
The final product of this project is a Guidance report (road map) for EU member states how to inventories vaccine resistant groups and for Public Health Authorities of the EU member states how to communicate with vaccine resistant groups in outbreak situations. This road map will be available at the projects website and will be distributed to MS through the European Centre for Disease Control.

Title:	**Monitoring acceptance national immunization programme (NIP) (together with ongoing project)**
Project number:	**S/210086**
Project leader:	Dr. H.E. de Melker (Hester) (CIb-EPI)
Start:	01-03-2011
End:	28-02-2013
Total SOR-budget:	€ 483,135

Motivation
The National Immunisation Program (NIP) is very effective as it succeeds in enrolling 90 to 95% of the parents into the vaccination programmes of children. Nevertheless, despite the success and the still high participation rates, public debate about vaccination is growing, critical parent groups arise, and more parents have doubts about the risk and benefits of vaccination. Currently the NIP is confronted with a development that is seen in other areas as well, namely a decreasing public trust in the advice of experts and a growing need of citizens to be involved in decisions that might affect their own or their children's health. Stated simply, there are two reactions to this development: a defensive one and a pro-active one. The defensive reaction implies claiming expertise and authority even harder than before, a pro-active one implies rebuilding trust and authority by investing in the relation with the clients to get insight in their needs to enable tailoring care to their situation. This proposal connects to the latter strategy since we expect the first one to be inadequate. From literature we know that there are two main feedback strategies for organizations and institutions: exit (turn to a competing organization of service) and voice (discuss the reasons for dissatisfaction). In the situation when there is no exit at all (like the service monopoly of the NIP) and when the service is a complex one (like health care), an organization is depending on voice to relate to the clients. From this we hypothesize that voice might be an important strategy to maintain the quality of the NIP in a context where vaccination is becoming contested.

In curative care the need of patients to be taken seriously has been addressed by a growing influence of patients in health care. It has been acknowledged that quality as well as effectiveness of health care will increase when structural feedback of patients is organized.

Against the background of these developments in curative care, NIP might learn a lot from observing the contact between parents and health care provider and feedback in vaccination practice. Room for voice provides the opportunity for parents to articulate doubts, to discuss bad experiences, to critize, etc. It will also provide a frame for re-interpretation of these items as well as addressing them by parents and professionals.
This proposal focuses on observing contacts between (future) parents and the health care providers in vaccination practice and performing interviews/conversations with (future) parents and health care providers. To do justice to the notion of voice as a public learning strategy and the fact that voice often develops hesitatingly, we organize the observations/interviews/conversations as a trajectory in vaccination practice with several contact moments.

Aim of the project
The aim of this project is get insight in the daily experiences and perspectives of (future) parents and health care providers, with whom the parents are confronted with, with regard to the vaccination practices by means of observations/interviews/conversations using a new method in a longitudinal setting.

Strategic and innovative aspects
This proposal is innovative for several reasons.
- The research method (responsive evaluation) is a form of 'action research', and differs from more traditional methods like trials in its scope: it is more about learning from experience and less about comparing groups defined in advance.
- It addresses a new problem of the NIP in a new way. It presents a unique opportunity for face to face contact with parents about their considerations and choices regarding the NIP, other than by internet or through third parties.
- It gives insight in the role of voice in other domains where the authority of expert advices has become contested and it is fruitful for studying experiment with voice in the chain-of-vaccination-care (midwives, child welfare centres).
- It is innovative as it explores a concept of learning about vaccination and risks among parents and professionals as a longitudinal process and not as a decision at one moment in time. It is also innovative in the sense that to empirically study the experiences with room for voice, the perspectives of the different stakeholders (experts, professionals and parents) are taken seriously.

Planned activities
- Reading literature, making contact with various people involved in the vaccination practice, short observations at midwife centre and child welfare centre, observation of two focus group interviews with parents (part of the project: 'Set-up monitoring acceptance NIP'), selecting and inviting (future) parents/pregnant women, preparing observation/interviews/conversations with parents.
- Fieldwork: observations/interviews/conversation with (future) parents and following of the 24 vaccination trajectories, analysing fieldwork.
- Interviews with health care providers, analysing interviews.
- Writing manuscript, giving feedback of the results to the participants.

Planned products
This study will give insight in the daily experiences and perspectives of (future) parents and health care providers, with whom the parents are confronted with,

with regard to the vaccination practices. The results of this study will be used in the set-up of the monitoring system for acceptance of the NIP. Peer reviewed publications.

Foreseen follow-up
The knowledge from this study may be used by different key persons (child health care professionals, programme manager NIP RIVM, Health Council, Ministry of Health, Welfare and Sport, communication department of RIVM) for communication with parents and health care providers and decision-making on possible changes in the (organization of the) NIP.

Title:	**Health literacy put into practice**
Project number:	**S/260206**
Project leader:	Dr. A.H. Uiters (Ellen) (V&Z/PZO)
Start:	01-01-2011
End:	31-03-2012
Total SOR-budget:	€ 88,300

Motivation
Socioeconomic health differences are a persistent problem in many countries. Clinical cohort studies and population-based health interview surveys have consistently identified education as one of the strongest and most consistent social determinants of health1. Nevertheless, the mechanisms via which education affects health outcomes remain unclear. A few recent studies have begun to provide evidence suggesting that literacy may be the key mediator on the impact of education on health2.
Health literacy builds on the idea that both health and literacy are critical resources for everyday living. Our level of literacy directly affects our ability to not only act on health information but also to take more control of our health. Health economists estimate that low health literacy alone costs the Dutch health care 61 million euro per year. More specifically, health literacy has been forwarded as a potential cost-cutting measure for more appropriate and responsible use of health care services.
It is increasingly recognized that one of the most serious limitations of the work in health literacy to date has been the dearth of empirical assessment tools for health literacy; in particular instruments which assess a larger range of competencies as expressed in the most widely used definitions of health literacy. Moreover, no agreement on the conceptualization and measurement of health literacy exists. Especially for the European situation almost no research experience on health literacy is available, as most of the research on this topic has been undertaken in North America. The proposed projects targets to address these existing knowledge gaps by means of assessing health literacy from a broad perspective in a joint effort with other European countries with special attention for the validity of the measurement.

Aim of the project
This project aims to contribute to the theory building and measurement of health literacy in collaboration with other European countries. This project will pursue the following objectives:
- To calculate a health literacy measure that can be put into practice in the Dutch public health and health care context.

- To compare the Dutch health literacy level and its key correlates with other European countries.
- To assess the construct validity of the health literacy measure.
- To translate the concept of health literacy and the results of this research into strategic action steps for the Dutch public health and health care system.

Strategic and innovative aspects
Health literacy is an emerging topic in European public health research. We can learn from the expertise build up in the USA and Canada, but the concepts and applications have to be adapted to our own national context and health care system. Putting the concept of health literacy into practice in public health as well as in health care could provide a useful tool to safeguard equal opportunities to health for all and equal care in the Netherlands.
This project brings together researchers from the public health/medicine and education sectors in European countries in their first official collaboration on health literacy. This collaboration will lay fertile ground to advance future work in the concept and measurement of health literacy. Performed in a comparative European approach, our project will not only document possible diversity in health literacy but also test the robustness of key correlates for health literacy across countries.

As mentioned before the proposed European project is complementary to the European Health Literacy Survey (EU-HLS). The EU-HLS involves, next to the Netherlands, Greece, Ireland, Austria, Poland, Spain, Bulgaria and Germany and will report its final results in 2011. The Netherlands is the only country who participates in both projects. Given the complementary character of both projects, for the Dutch situation health literacy can be studied from a broad perspective, facilitating more profound conclusions about the level of health literacy, important determinants and possible leads for improvement. This places the RIVM in the unique position of being one of the European predecessors in the field of health literacy. Furthermore, with this project the national and international role of the RIVM in the field of health literacy can be enlarged, as it offers the opportunity to intensively collaborate with the international founding fathers of the scientific work on (health) literacy.

Planned activities
- To calculate a health literacy measure that can be put into practice in the Dutch public health and health care context.
- To compare the Dutch health literacy level and its key correlates with other European countries.
- To assess construct validity of the health literacy measure.
- Translate the concept of health literacy and the results of this research into strategic action steps for the Dutch public health and health care system.

Planned products
Final products of the project will be a scientific publication on health literacy and a chapter in a European report targeting stakeholders. This project will contribute to strong national and international collaboration on the field of health literacy.

Foreseen follow-up
This project will allow the RIVM to keep up to date with and to gain an expert position in the field of health literacy research. Results from this project will be translated into interventions to improve health literacy in order to consolidate the equal access to care as well as the quality of care for disadvantaged groups

and hence inspire the national policy plan to address socioeconomic and ethnic health differences. The expert position of the RIVM with regard to health literacy will improve the future support we provide for the Ministry of Health, Welfare and Sport in its development of a sustainable health care system. For example, new assignments to further develop programmes to implement the national strategy to address health disparities.

Title:	**Factors influencing willingness to participate in preventive interventions: discrete choice experiments**
Project number:	**S/260216**
Project leader:	Dr. G.A. de Wit (Ardine) (V&Z-PZO)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 582,000

Motivation

Participation in preventive programmes, such as lifestyle improvement programmes and vaccination programmes, is essential to reach effectiveness and cost-effectiveness of such programmes. In practice however, the willingness to participate is in general low (lifestyle programmes) or declining (vaccination programmes). For all preventive programmes, it is important to have knowledge about the factors that contribute positively to participation.
In the current project, we have chosen three different preventive programmes for which implementation issues probably will be important in the next few years.
Knowledge obtained with this project will help RIVM in supporting health professionals and in designing preventive programmes that optimally suit participants needs.

Aim of the project

We propose to study the factors underlying the willingness of target group members to participate in preventive interventions.
Specific aims are to:

- Perform three Discrete Choice Experiments (DCE's):
  - on lifestyle interventions for diabetes type 2 patients.
  - in parents of newborns for a rotavirus vaccination programme.
  - in parents of newborns for blood spot screening.
- Measure the influence of 'co-payment' versus 'bonus' on the willingness to participate in a lifestyle intervention and of 'co-payment' in the vaccination programme (as bonuses are no option in vaccination programmes).
- Perform research on the relative performance of different methods to elicit preferences (e.g. mini-labs, individual interviews, internet questionnaires).

In the DCE's, we will include members of groups with lower socioeconomic status and people with different ethnicity, since they are most difficult to reach with preventive health programmes and knowledge on factors that may increase participation in those groups is much needed.

Strategic and innovative aspects

At the moment of writing, the three examples DCE as described seem most relevant with regard to future policymaking. From a scientific point of view, the project is challenging, as DCE techniques have hardly been used in the field of health promotion and lifestyle improvement, and never for rotavirus vaccination

and neonatal blood spot screening. As RIVM's tasks are moving fast towards communication with new target groups (e.g. public health professionals, Municipal Health Services), the results of this project will be helpful in optimizing communication strategies. Implementation of and communication on future preventive programmes will benefit from the methodology and knowledge that will be obtained from this research project. The project will enhance the process management role that RIVM has in the fields of vaccination, healthy living and population screening.

Planned activities

We propose to conduct three DCE studies, one among diabetes patients, one among parents of target groups (newborns) for rotavirus vaccination and one among (future) parents of newborns for blood spot screening. The DCE's will be performed in succession, in order to learn from experiences and to be able to include newest methodological insights in the second and third DCE. The DCE's will be conducted according to a recently published users guide of Lancsar and Louviere. Within the four-year PhD project as proposed, 16 months will be available for each DCE on average. Each DCE will consist of four phases:

- Phase 1: Selection of relevant attributes.
- Phase 2: Pilot testing of questionnaire.
- Phase 3: Data collection.
- Phase 4: Data-analysis and reporting.

Planned products

At least five publications (one for each DCE, one on the role of price proxies and economic incentives, and one on the relative performance of different elicitation techniques) will be published in international peer reviewed journals. The project will results in a PhD thesis. Also, RIVM may use the results of knowledge derived within this project in its process management role. We propose to organize workshops within and outside RIVM (e.g. for Regional Health Authorities and health promoting institutes). Furthermore, presentations and workshops about the study results will be given at national and international conferences.

Foreseen follow-up

The knowledge from this investigation will be relevant for different sectors and different labs of RIVM. Both Centre for Infectious Disease Control (CIb) and the sector Public Health & Care (V&Z) can use knowledge from this project while designing and implementing future preventive programmes. Also, the results of this project may be used in advising intermediary parties in the field of health promotion and prevention, such as regional health authorities and local governments.

Title:	**Combining resources in health care: How can we prepare our human resources to exploit our technical resources?**
Project number:	**S/260286**
Project leader:	Dr. M.S. Lambooij (Mattijs) (V&Z-PZO)
Start:	01-04-2011
End:	01-04-2015
Total SOR-budget:	€ 408,900

Motivation

In a recent report, the health care innovation platform, (Zorginnovatieplatform, ZIP) concluded that more attention is needed for the connection between the needs in health care and labour saving technology. Use of new technologies by health care workers may help to solve the problem of labour shortage and may at the same time improve quality and efficiency of health care. However, the adoption of innovations in health care has been found to be slower than desired. For instance, the number of users of the national Electronic Patient Records still lags behind expectations.

There are indications that in various fields in that adoption of innovations are hampered because personnel do not feel that adopting the innovation is beneficial for them or their work. In turn, this may negatively affect patient safety and quality of care. We know for instance that computerized clinical decision support systems reduce medication error rates. This shows that a slow adoption rate of useful technology may be a missed opportunity to improve health care.

The Ministry of Health, Welfare and Sport argued that the culture in health care institutions is a mayor driver for implementation of innovations. Scientific evidence of the last decades revealed a multitude of factors that affect adoption of innovations. These aspects range from characteristics of the new technology to the environment in which the technology is adopted. A study on the adoption of guidelines in health care, which can be compared to adoption of innovations, revealed that knowledge and motivation, availability of support staff, access to facilities and education of staff and patients were factors influencing the adoption of guidelines. Implementation of guidelines is also affected by its features, features of the target group, features of the social context/setting and features of the organizational setting. A review study also identifies the softer aspects such as culture and climate, leadership style, power balance, social relations and attitudes of health care personnel. But also the health care organization in itself causes barriers on various organizational levels.

Aim of the project

This project aims to increase the existing knowledge on barriers and drivers of the adoption of technological innovations in Dutch hospitals. We will focus on ICT-related innovations in hospitals. Examples we will consider for inclusion in our constructive technology assessment (CTA) are telecardiology, teledermatology, picture archiving and communication system (PACS), decision support systems and related information systems. These types of innovations may increase quality of care, improve service levels for patients, may help avoid errors in the medical process and may help avoid redundant work by the health care professionals. ICT related innovations in the hospital setting will be evaluated on potential benefits and costs. Subsequently we will focus on the interaction between organizational aspects, social aspects and person-related aspects that form drivers or barriers of these innovations.

Strategic and innovative aspects
The innovative nature of this project is that cooperation takes place between the RIVM, which is mainly concerned with 'hard' measures in health care research and the department of Organizational Psychology (University of Twente), which has much expertise in measuring 'soft' aspects such as human behaviour, attitudes and culture. In line of this the strategy of the University of Twente is to combine 'human touch and high tech'. As such the RIVM will gain knowledge that is still scarce and necessary to have to provide answers on the role of innovation in health care.

Planned activities
- Analyse potential effects of medical technology based on medical, social, economical and social factors relevant to the decision-making the stakeholders in deciding to adopt an innovative concept, using constructive technology assessment.
- Literature research.
- Development and testing of questionnaires, vignettes and interviews.
- Data collection.
- Data analysis and writing of articles.
- Participation to international congresses.

Planned products
- Database use of innovations in hospitals. The database will contain data of 10 Dutch hospitals; and per hospital 10 departments and 25 employees in every department. The dataset will contain information on management practices, HR practices, cultures of hospitals, leadership styles, professional attitudes of health care workers, commitment of health care workers and, social structure, professional attitude, affective organizational commitment.
- Five peer reviewed publications.

Foreseen follow-up
The knowledge of this project ads to the knowledge base of the RIVM and is in particular relevant to research related to health care performance. It will help the RIVM to serve the clients to answer questions regarding developments in health care.
Use of technology is expected to reduce the upcoming labour shortage in health care. Knowledge and research experience on this topic is therefore relevant in order to answer questions of policymakers.
Health is influenced by all sorts of human behaviour, ranging from life style to adopting of innovations by health care professionals. Knowledge of the interaction between human behaviour and its (technological) environment will increase understanding why policies on national level will or will not influence health of the general public. With this knowledge, RIVM will increase its capacity to serve the Ministry of Health, Welfare and Sport.

Title:	**Evidence to inform policymaking in public health**
Project number:	**S/270196**
Project leader:	Dr. M. van den Berg (Matthijs) (V&Z/VTV)
Start:	01-01-2011
End:	31-12-2013
Total SOR-budget:	€ 313,600

Motivation

The Ministry of Health, Welfare and Sport has adopted effectiveness of preventive interventions as a paradigm in health policy decisions (VWS, 2007). Effectiveness concerns the appraisal of four aspects: relevance, direction and magnitude of the effects of interventions, and the quality of the studies. As this is a very complicated consideration, policymakers depend on so called 'trusted sources'. This means that someone else other than busy front line policymakers – preferably a trusted public sector organization like the RIVM – does the selection and critical appraisal. The main concern of this project is the usefulness of the results of our critical appraisals of studies on the effectiveness of public health interventions for policymakers and for public health professionals.
This fits well in an international development, which is referred to as 'evidence-informed health policymaking' (EIHP). EIHP is an approach to policy decisions that aims to ensure that decision-making is well-informed by the best available research evidence. It is characterized by the systematic and transparent access to, and appraisal of, evidence as an input into the policymaking process.

The overall process of policymaking is not assumed to be systematic and transparent and evidence-based. However, within the overall process of policymaking, systematic processes are used to ensure that relevant research is identified, appraised and used appropriately. In this project we focus on the appraisal process and the formulation of sound recommendations, rather than on the policy process itself.
For the RIVM it is essential to be seen as a trusted source by policymakers and public health professionals. Therefore our critical appraisals should be transparent en unambiguous. Currently, the communication about effectiveness in the division's products is suboptimal. It shows different approaches. This project aims to improve and harmonize the RIVM's communication about effectiveness by presenting explicit standards for appraisal of the four aspects of effectiveness (relevance, direction, magnitude, quality).

Aim of the project

There are two aims of the project. The first aim is to improve and harmonize RIVM's public health and health services divisions communication about effectiveness of prevention in public health. The second aim of this project is to improve the usefulness of our information on effectiveness for health policymakers and public health professionals. With useful we mean valid (from a 'trusted source'), relevant and easy to administer.
Specific objectives are:

- To review recent RIVM reports, papers and websites focusing on the different ways of appraisal and communication of effectiveness information.
- To become trained and experienced in grading and communicating evidence for use in health policymaking.
- To develop and implement standards for the appraisal and communication of effectiveness of public health measures.

Strategic and innovative aspects
The strategic interest of the project is that the RIVM will strengthen its position as a trusted source for local and national policymakers and professionals. We will learn from international developments on EIHP. At the end of the project the RIVM will be an active participant in some of these international expert groups. We will strive for harmonizing several national appraisal systems on the effectiveness of public health interventions.
The innovative nature of the project is that we do not try to implement old fashioned evidence based policymaking. We acknowledge the fact that effectiveness is rarely the only criterion for public health decision-making. Instead, decision-makers usually also weigh several other aspects, for instance feasibility, recourses and local context. The format and content of the information on effectiveness in our products should facilitate this more elaborate appraisal process. That is exactly what evidence-informed policymaking is about.

Planned activities
- Analysis of division's effectiveness communication, learn from related initiatives, develop draft standards and support changes in the appraisal criteria and system of RCI.
- Pilot of draft standards in three regular projects.
- Discuss, adapt, finalize, and implement standards.

Planned products
Product will be a RIVM-report, in which the analysis of the current effectiveness information and appraisal systems in a range of RIVM-products will be described. This report will include the results of the interviews among the users involved.
Standards for the appraisal and communication of evidence to inform policymakers in public health will be developed and published in both a peer reviewed paper and an internal web tool. The paper and the web tool will serve as a reference frame for future reports and websites.
The results of the project will also be presented at national and international conferences. Furthermore, at the end of the project the RIVM will participate in some of the international expert groups in this field.

Foreseen follow-up
On the completion of this project current best practice approaches for evidence informed policymaking in public health will be used. This implies harmonization and providing a richer context of those approaches that until date have been used in RIVM, most often in a more isolated or restricted sense. This will result in an increased convergence and reduced contradictions of reporting of research results in RIVM products. The workshops, lectures, discussions, the standards and the in-company training sessions will support a growing consensus about this way of communicating effectiveness in our division. The standards will be used in regular RIVM-projects on the effectiveness of public health interventions. The outcomes will be used in at least two important products of the division: the Public health status and forecast report (PHSF) 2014 and the Quality-programme healthy living.

In a follow-up project we propose to monitor the use of the set of standards. In that project we will search for consensus on evidence to inform policymaking with other divisions of the RIVM. For this reason, two other divisions are involved in the advisory board of this project.

Title:	**Improving knowledge utilization**
Project number:	**S/270206**
Project leader:	Prof. dr. ing. J.A.M. van Oers (Hans) (V&Z/VTV)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 474,800

Motivation

New communication methods and increased workload drastically changed the way policy officers nowadays communicate and meet their information needs. These developments make that RIVM has to change its current way of presenting research information and knowledge to policy officers, to maximize utilization in the policy processes. This applies especially for those RIVM-reports that are by nature close to the policy processes at VWS.

Both the Volksgezondheid Toekomstverkenning (VTV; Public health status and forecast report, PHSF) and the Zorgbalans (Health care performance report; HCP) are very 'close-to-policy' at VWS. To maximize the policy effectiveness of the 2014 editions of these reports, it is necessary for RIVM to invest in improved knowledge utilization.

Another category of 'close-to-policy' reports is formed by the regular advices produced by the RIVM expertise field 'Medicinal products and Medical Technology (GMT)'. It is not always clear whether the advices generated are indeed utilized in policymaking, what factors influence the utilization of an advice report and what arguments have been used to adopt an advice or not.

In conclusion, outcomes from all these reports have to end up better in the policy domain — by a better harmonization of activities between the RIVM and the commissioners — and within that policy domain have to contribute more effectively to policy processes. In the translation of knowledge into policy many actors and factors play a role. Insight into this helps RIVM to make the future PHSF, HCP, and the reports in the GMT expertise field (and other 'close-to-policy' reports) more effective e.g. by a better gearing of the needs of policy officers and the data generated by the RIVM or by presenting the data in a different way.

Aim of the project

The aim of this project is to improve knowledge utilization from RIVM reports in agenda setting, policy development and policy monitoring. The objectives of this project are to:

- Map in detail how and to what extent knowledge from PHSF 2010, HCP 2010 and a selection of advices generated in the GMT field is used in agenda setting, policy development and policy monitoring at the national level.
- Identify along the lines of a theoretical framework the most decisive factors and actors that promote and inhibit utilization of knowledge from these reports.
- Gather practical information on the use of new (communication) methods/tools (e.g. internet networks, communities, etc.).
- Prepare a draft manual/set of guidelines to improve knowledge utilization, based on the theoretical framework, the empirical findings to further specify and concretize this framework, and on the practical information on new (communication)methods.
- Evaluate this draft manual/set of guidelines during production and implementation of PHSF 2014, HCP 2014 and future advices generated in the GMT expertise field, to make these reports more policy effective.
- Develop courses/meetings for RIVM project leaders to effectively implement the final guidelines within the RIVM.

Strategic and innovative aspects

In recent years the interest in research utilization in the field of public health has grown, among scientists and policymakers. It is recognized worldwide that knowledge utilization in public health policy is often cumbersome. Many countries produce high quality public health reports, but little is known about effective ways of translating this knowledge into policy. Knowledge about knowledge utilization is scarce, inside and outside RIVM, and rarely tailored to real life situations. Empirical or even descriptive studies are rare.
This SOR project provides direct applicable knowledge for enhancing the policy effectiveness of 'close-to-policy' RIVM reports, and in this way contributes to the strengthening of the position of RIVM. Furthermore, this project supports and improves the development of 'Evidence Informed Health Policymaking'. Finally, the study contributes to the (relatively scarce) scientific knowledge in the field of knowledge utilization.

Planned activities

The study design will be organized along the case study methodology. The theoretical framework for this study is based on a recent international literature review in the field of public health knowledge utilization.
The interaction model is generally regarded as the main explanatory model in explaining knowledge utilization in health policy, and will therefore be used in this study. However, in the first phase of the project it will be considered whether this model needs to be adapted to the specific Dutch public health context.
In 2010, as a pilot study, a questionnaire based on the above mentioned dimensions was developed and tested on the HCP 2008, and is available for this study.
Planned activities are:

- The literature concerning knowledge utilization models and knowledge utilization measurement will be studied, in order to check the necessity of adaptation of the theoretical framework to the Dutch situation.
- Processes, networks and the extent of knowledge utilization in the policy processes following the publication of PHSF-2010, HCP-2010 and a selection of advices generated in the GMT field will be described in detail.
- The identified factors influencing the uptake of knowledge (on both the individual and environmental level) will be judged on their relevance and changeability. Next, (evidence based) interventions will be selected for enhancing knowledge utilization. This step from insight in determinants of behaviour to interventions effectively facilitating the use of knowledge is therefore an important focus of this study. These results form the basis of a first draft of a manual, containing a set of guidelines for RIVM researchers to improve knowledge utilization from 'close-to-policy' reports.
- These draft guidelines are evaluated during production and implementation of PHSF 2014, HCP 2014 and GMT advices generated in 2013. In 2013 the usability is tested, and in 2014 using Knott and Wildavsky's 'ladder of utilization' the knowledge utilization of the RIVM products in the policy processes will be measured again, to evaluate the effectiveness of the measures taken.

Planned products

The main results of this project are:

- A manual/set of guidelines for RIVM-researchers to improve knowledge utilization for future 'close-to-policy' products, based on the actors and factors identified and the gathered information on new communication methods/tools, evaluated on its usability and effectiveness.

- Intensive courses/meetings for RIVM experts/project leaders on knowledge utilization.
- Publication of the results in several international articles, resulting in a PhD thesis.
- Detailed practical and theoretical understanding of factors and actors that improve knowledge.

Foreseen follow-up
With the knowledge generated within this project, RIVM can maximize the policy effectiveness of its 'close-to-policy' reports, and in that way maintain and enhance its national and international leading position regarding e.g. the PHSF and HCP. The project will improve cooperation between the Ministry of Health, Welfare and Sport, Inspectorate and RIVM (and the other partners involved), and will lead to strengthening of interaction, greater mutual understanding, and better knowledge of each other's networks. This will also lead to a higher societal impact of the knowledge generated by the RIVM.

Title:	**CBIs childhood obesity**
Project number:	**S/270246**
Project leader:	Verschuuren, mw. dr. M. (Marieke) (V&Z/VTV)
Start:	01-01-2011
End:	31-12-2012
Total SOR-budget:	€ 45.800

Motivation
Overweight and obesity are rising dramatically, particularly among European children, having a striking impact on their health. Actions at the local level, mainly targeting children, can be effective in improving health behavior in the long run.
The EU Platform on Diet, Physical Activity and Health explores actions for improving nutrition and physical activity, which involve the participation of a number of EU level organizations representing economic operators, the leisure sector, public health and consumer organizations.
Sustainable mobilization of local stakeholders is required to create the conditions and relevant environments to support healthier lifestyles for children and their parents. The European Union public actions in these areas aim at complementing and optimizing actions undertaken at other decision-levels, national or regional, as well as facilitating the sharing of methods and successful approaches across Member States.

Aim of the project
The European Commission has identified the need for a comprehensive overview of the different types of local community approaches to reduce childhood obesity. There are a lot of activities currently carried out at local level, focusing on childhood obesity reduction, some funded partly by the European Union budget, others funded by Member States, and some funded privately or by a mixture of those.
The aim of this request for specific services is to collect information on Community Based Initiatives (CBIs) to reduce childhood obesity. Facilitating access to such information should help to exchange experiences and facilitate the creation of new initiatives based on proven practices.

Strategic and innovative aspects
The strategic added value of this project is related to the strong international context. There is close cooperation with both the European Commission (EC) and WHO-Euro. This will allow RIVM to contribute to the policy goals of the EC and WHO in the highly policy relevant area of obesity, and to internationally present RIVM as a centre of expertise in the field of (assessing quality of) preventive interventions. The series of presentations for platforms such as the High Level Group for Nutrition and Physical Activity, which are also part of the products that need to be delivered in this project, will also help to strengthen the international position and reputation of RIVM.
This project is innovative because a Europe-wide inventory with a specific focus on Community Based Initiatives (CBIs) targeting childhood obesity does not yet exist. As such it will fill a gap in information and result in a lot of new insights regarding the types of CBIs implemented in Europe and their quality.

Planned activities
Fase 1:
- Map existing inventories of CBIs/CBI-like approaches, make draft inception report.
- Kick-off meeting, delivery of final inception report, prepare data collection (make questionnaires, mobilize networks, refine national search strategies).
- Data collection, develop skeleton report, interim meeting.
- Data analysis, write report.
- Write report, submit draft report.
- Review of report, process comments reviewers.
- Submit final report.

Fase 2: Possible presentations for stakeholders at the request of the Commission.

Planned products
- Series of 4-6 presentations to EAHC, DG SANCO and other forums when requested by EAHC/DG SANCO. The RIVM team will prepare one 'core' presentation in which context, methods and result of the project will be described. This presentation can be used by the Commission, and/or modified by the RIVM team to make it suitable for specific audiences. The members of the RIVM team will be available to give presentations during month 11-14 of the project.
- Final report which will be prepared both in paper and electronic form.
- Database containing all data gathered in data collection phase.
- Article in scientific peer reviewed journal.

N.B.: The products marked by the first 3 bullets are in the contract with the European Commission. The Product marked by the last bullet is a separate product that will be delivered for SOR.

Foreseen follow-up
Through the strong international dimension, this project might result in a stronger international position of RIVM as a centre of expertise in the field of preventive interventions/assessment of quality of interventions/obesity. In turn this will potentially result in better opportunities for obtaining new grants/commissions and for new international collaborations.
WHO-Euro will make available the database and The European Commission will publish the report that will be produced within the project on their website. Furthermore, project results will be disseminated through a series of presentations (at the request of the European Commission).

4 Healthy ageing (HEA)

4.1 Strategic aims

Societal impact
Health is important to everyone of us, we all hope to live long and healthy lives. Hardly a day goes by without headlines touching on issues related to health and ageing: politicians discuss increasing the retirement age or health experts see growing numbers of ageing-related illnesses such as diabetes. In recent years, the Netherlands lost its top ranking among European countries in terms of healthy life expectancy.

The occurrence of comorbidity (the simultaneous appearance of multiple diseases) among senior citizens is increasingly turning out to be the rule rather than the exception. On the one hand, societal development such as the 24-hour economy, the augmentation of stress and burn out symptoms and *lifestyle* changes are likely to be connected with the rise of comorbidity. On the other hand, genetics play an important role: with healthy parents a citizen is more likely to age in good health. In order to design effective interventions we depend on knowledge about the factors and mechanisms (from cell to society) that lead to healthy ageing.

Society puts growing emphasis on people's personal accountability. More than before, individuals are challenged to take responsibility for (the preservation of) their own health. However, to be able to make the right choices, they need access to adequate information.

Description and impact in relation to RIVM tasks
Healthy ageing touches upon many aspects of RIVM's mission. At a personal level, ageing citizens are more vulnerable to diseases, such as seasonal flu. They may also be more susceptible to environmental risks, such as environmental contamination, lower immunity against infectious diseases, or a rise in allergies against various consumer products.
Ageing populations should not be considered as one homogenous target group; they vary significantly in terms of ethnicity, cultural background, socioeconomic status or regional environment. Obviously, this context requires extra attention.

Ageing research is not a simple task due to the stretched time spans between visible effects. Today ageing populations have different characteristics than ageing populations had 20 years ago, as well as ageing populations in 20 years will differ from ageing populations now. This problem is not a unique Dutch concern; many other countries face similar ageing-related problems, and learning from and working with those countries will provide very valuable insights.

Focus and future direction of projects
As the research theme's name (Healthy Ageing) implies, emphasis will be put on prevention. One of the primary tasks of the RIVM as a government agency is to contribute to effective interventions.
We already know that lifestyle and nutrition play an important role in the origins of chronic diseases. This does not only concern lifestyle and nutrition of the elderly; healthy behaviour starts at a younger age. It is important to study the impact of behaviour on ageing throughout all phases of life.

Epidemiological research strongly contributes to this research theme, including research into ageing and chronic disease mechanisms and the connected determinants of elderly people's susceptibilities.

Past epidemiological and animal research has resulted in substantial knowledge about ageing. The research activities in the scope of this Strategic research theme aim to complement and connect the existing knowledge base. New insights can contribute to the improvement of intervention strategies. The Doetinchem Cohort Study (a long-term study that targets population groups in the town of Doetinchem), which is available to RIVM-researchers, offers the unique opportunity to access information over a period of 20 years.

Within this Strategic research theme specific attention will be dedicated to the elevated susceptibility of ageing citizens: which factors determine the susceptibility of ageing people? The design of effective interventions also requires knowledge about the composition of ageing groups in the future as well as cost-benefit analyses of prevention efforts. Further focal points include multiple medicine use by senior citizens, the occurrence of comorbidity and malnutrition, as well as potential coherence between these factors. Moreover, current research question is to investigate the actual cover of special needs of elderly citizens, for example regarding diagnostics. The development of adequate screening methods for community health centres could significantly improve these diagnostics.

Although 'health' encompasses more, in this research theme emphasis will be placed on physical well-being. Broader research proposals will need to fit within RIVM's core tasks and offer opportunities for interventions at the community level.

Within the Netherlands, the RIVM is not the only player in the field of ageing research: the universities of Leiden, Rotterdam, Wageningen and Maastricht as well as the Vrije Universiteit Amsterdam also perform research in this field. The establishment of cooperative networks within projects increasingly occurs for complementary research purposes or out of need to share resources. Within these networks, the RIVM covers the niche area of improvement of intervention methods, whereas universities tend to cover the more fundamental research activities.

International connections
The Healthy Ageing research theme will provide ample opportunities for international cooperation. 'Healthy ageing' is among the midterm strategic priorities of the World Health Organization (WHO). Similarly, the European Commission's Directorate-General for Health and Consumers (DG SANCO) has identified 'fostering good health in an ageing Europe' and 'promoting health of older people' as priorities.

In its 2010 Work Programme, the EU's 7th Framework Programme (FP7) mentions 'Human development and ageing' as a priority. Under FP7's Health theme, a call has been issued for Joint Programming initiatives to combat neurodegenerative diseases, in particular Alzheimer's disease.
The EU's 'Second programme of Community action in the field of health' (2008 to 2013) also lists the effects of ageing as a priority. Most certainly, additional international calls for proposals related to the Healthy Ageing research theme will be published, enabling a connection to RIVM projects.

Keywords
health, life style, cost, benefit, healthy nutrition, food additives, living environment, working environment, chronic diseases, epidemiology, interventions, waning immunity, susceptibility, antibiotics resistance, related infections, alcohol, drugs, pharmaceutics, multimorbidity, comorbidity, risk factors, physical impairments, biomarkers, population screening

4.2 List HEA

Number	Title	Project leader	Int.
S/210216	Willingness of elderly to vaccinate	Hester de Melker	
S/260226	Life course approach to ageing	Susan Picavet	
S/260236	Healthy vascular aging (The impact of lifestyle on diabetes, cardiovascular and kidney diseases and cognitive decline: a life course approach)	Monique Verschuren	
S/260306	Early origins of disease	Alet Wijga	
S/270216	Determinants of social participation in old age	Petra Eysink	
S/340005	Monitoring human ageing	Martijn Dollé	
S/340006	Are supplements good for healthy ageing?	Eugene Jansen	
S/340007	Fetal origin of adult disease	Leo van der Ven	
E/340032	Cofinancing for CHANCES	Euhene Jansen	*
E/340100/01/SO	DNA repair, mutations and cellular aging	Martijn Dollé	*
S/350050	Biomarker associated dietary patterns for improving health of the elderly?	Jolanda Boer	
S/370002	Adequate medication use by elderly outpatients	Diana van Riet - Nales	

Int. = international project cofinanced by SOR-budget

4.3 Summaries

Title:	**Willingness of elderly to vaccinate**
Project number:	**S/210216**
Project leader:	Dr. H.E. de Melker (Hester) (CIb-EPI)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 527,824

Motivation
The Dutch population is ageing very fast. It is expected that in 2050 a quarter of the population will consist of persons 65 years old and over; in 2009 this percentage was 15%. It is expected that more elderly will take actively part in our society. This will result in more social contacts which may increase the risk of (transmission of) vaccine preventable diseases (VPDs). Furthermore, it is known that elderly are more susceptible to several infectious diseases compared to younger persons due to gradual deterioration of the immune system brought on by ageing, i.e. immunosenescence. In addition, elderly could suffer more from an infection due to underlying chronic diseases, also called comorbidity. Furthermore, due to general fragility (e.g. reserve capacity of organs is reduced at older age) the risk on a severe course of disease is higher. Demands on health services and related costs will clearly rise as a result of this demographic change. Successful (re)vaccination of elderly against important infectious pathogens (e.g. pneumococcal disease, herpes zoster, pertussis, *Haemophilus influenzae* type b, hepatitis A) may be a major preventive strategy for reducing health care demand. Until now the only vaccination routinely offered to elderly above 60 years of age is against influenza (coverage amounts to 77%).
One of the major questions regarding the potential improvement of health of elderly through vaccination with currently available vaccines is the acceptation of such an intervention among elderly. Therefore, before implementing new vaccination strategies, knowledge on acceptance of vaccine uptake and determinants that influence uptake is of utmost importance. While our knowledge on factors influencing the acceptance of childhood vaccination is limited, data on this topic for elderly is even scarcer.

Aim of the project
The aim of the proposal is to construct a generic model with which it will be possible to estimate the willingness to accept vaccination against different vaccine preventable diseases among various age groups of elderly (60 years old and over) and the relative importance of the factors determining the willingness to vaccinate. For this purpose we will use multi criteria analyses.

For diseases for which a vaccine is currently available and that are of interest for elderly (e.g. pneumococcal, hepatitis A, herpes zoster, pertussis, *Haemophilus Influenzae* type b we will review the following information to assess potential determinants of willingness to vaccinate:
- Age-specific risk on the disease among elderly.
- Disease severity among elderly.
- Characteristics of vaccines, currently available for elderly.

To collect information on other potential relevant determinants (e.g. possibility visiting GP, recommendation vaccination by general practitioners (GPs), etc.), literature will be reviewed and focus group interviews among elderly, GPs and possibly other experts (such as geriatricians) will be performed.

In addition, focus group interviews will be used to select which determinants should be incorporated in a Discrete Choice Experiment (DCE), which involves choices between scenarios describing various levels of the determinants that influence willingness to vaccinate (i.e. various levels of vaccine effectiveness or disease severity). Data collected in the DCE will be assessed and analysed with a conditional multinomial logic model (based on the random utility theory). This will enable the prediction of the willingness to vaccinate and the relative importance of each determinant.

Strategic and innovative aspects

Knowledge on willingness to vaccinate among elderly is largely lacking. With growing numbers of elderly, the availability of adult booster doses and the continuous threat of several target diseases, this proposal aims to fill this knowledge gap. Essential factors that influence the willingness to vaccinate, such as the prevalence and risk of contracting disease, disease severity and vaccine characteristics have mainly been addressed for routine childhood vaccination but are unknown or have not yet been fully explored for elderly. Currently, only vaccination against influenza has been routinely offered to those 60 years old and over, with a yearly uptake of about 77% of the targeted group. With presently available vaccines more health gain can be achieved for other target diseases. These diseases are expected to be more prevalent due to rising numbers of elderly people. The potential success of decreasing the disease burden in elderly through vaccination heavily relies on vaccine uptake. Knowledge on factors determining this uptake is therefore of utmost importance.

Planned activities

- Literature study on vaccine acceptance among elderly.
- Performing focus group interviews among elderly and GPs.
- Collecting data from various sources on disease severity, disease incidence, vaccines.
- Estimating age-dependent risk of contracting different VPDs among elderly.
- Summarize the results of the literature review and focus groups interviews aiming to show that vaccine acceptance needs further study such as proposed in second to fourth year.
- Analysing and reporting results from focus group interviews.
- Recruiting small sample of respondents, construct, perform and analyse pilot DCE-experiments.
- Adapting and performing main DCE survey.
- Analysing results from main DCE and constructing generic model (multicriteria analyses).

Planned products

- A generic model with which it will be possible to predict/estimate the willingness to vaccinate among elderly not only for existing VPDs (such as pneumococcal disease, *Haemophilus Influenzae* type b, herpes zoster, pertussis, and hepatitis A) but also for future VPDs with their own specific levels of the attributes.
- Overview of the incidence and severity of the above mentioned target diseases in elderly and characteristics of vaccines which are currently available for elderly.
- Approximately five papers intended for peer reviewed journals.
- PhD thesis.

Foreseen follow-up
The results of this study may be used by different key persons (programme manager NIP RIVM, Health Council, Ministry of Health, Welfare and Sport) for decision-making on possible introduction of vaccinations for elderly, including serving as an important input into future cost-effectiveness analyses. Furthermore the information will be used to improve communication (RIVM, GP, other physicians) on prevention of infectious diseases among elderly through vaccination. This study is likely to have spin-offs in the judgment on participation issues for other preventive measures outside the field of vaccination.

Title:	**Life course approach to ageing**
Project number:	**S/260226**
Project leader:	Dr. H.S.J. Picavet (Susan) (V&Z-PZO)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 464,101

Motivation
We all want to grow old healthy, but how and when is it necessary to take action? Do we have to live a healthy life during the full life course or is it enough to start a healthy life at age 40? Or is life style around the age of 20 crucial for healthy ageing? How many persons change their life styles during the life course and what does it mean for our health at older age? And are these changes linked to specific stages or moments of life like marriage, having children, becoming diagnosed with a chronic disease, losing a partner or retire from work, because these stages might be attractive for interventions for prevention? There is a growing evidence that influences during the total life course affect old age health. Factors in utero (e.g. low birth weight), infancy (e.g. maternal attachment), childhood (e.g. diet), adolescence (e.g. smoking) and adulthood (e.g. body mass index, BMI) are shown to be risk factors for chronic diseases and disability at older age. The current research focuses on the (pre)adult life origins of healthy ageing with the following characteristics:
- Healthy ageing refers to being non-disabled with an adequate quality of life.
- Adolescent and adult life origins with a relevance for public health and prevention: these are mainly life style related (physical activity, smoking, alcohol consumption, diet).
- The life course is defined by age or by stage of life (related to education, work, family or health problems).

Aim of the project
The general aim is to provide insight into life style changes over the (pre)adult life course and to show how these affect disabilities and quality of life in old age in order to find clues for prevention related to healthy ageing. The project has the following three objectives:
- Determine the role of stages of life for changes in life style.
- Explore how changes in life style over the adult life course affect health at old age, in particular disability and health-related quality of life.
- Identify the possibilities to improve the development and/or timing of life style interventions in the Netherlands using the life course perspective.

Strategic and innovative aspects
The central research question of Healthy Ageing is: what makes the elderly walk, climb a flight of stairs, do their groceries, get in or out their chair or bed, carry out their daily activities, and can they do this with a sufficient level of quality of life, irrespective of existent chronic diseases *and* to a high age as possible? The current study will provide new insights in this core public health question, by providing information on the impact of life style during the life course on old age health.
Life course epidemiology is a relatively new research area which is expected to enrich our thinking of public health and healthy ageing. A focus on and division in stages of life and life events can be fruitful to explain life style differences and may be useful to find new opportunities for prevention of unhealthy behaviour, by focusing on critical periods and critical transitions.

Planned activities
- A systematic review of the literature.
- Data analyses of large-scale cohort data in the Netherlands (Doetinchem Cohort Study (DCS) and the Longitudinal Aging Study Amsterdam (LASA).
- Most available life style interventions in the Netherlands, (>4000) are described in a database of the RIVM's Centre of Healthy Living (CGL) with information on the content, target groups and effects. Based on this Intervention(I)-database, an overview will be made on how transitions in the life course are taken into consideration in current prevention strategies.
- National expert meeting to identify possibilities to improve the design of life style interventions in the Netherlands.
- We will identify gaps and overload in interventions for some stages of life. This will give direction toward the development of a more coherent package of interventions throughout the life course.

Planned products
- Three peer reviewed publications on life style and stages of life.
- Knowledge and insights from the project on the life course changes and health status and the impact on the design of health intervention will be integrated in the Dutch Public Health Status and Forecast of 2014, the National Public Health Compass and Loketgezondleven.nl.
- A specific report (in Dutch) with advice on possibilities to improve life style interventions by incorporating insights from life course perspective.
- The data on transitions in life style over the life course will also be used as input for new versions of the RIVM's Chronic Disease Model in order to improve public health modelling exercises.
- The results of the project will provide input to improve the measurements in the next round (6th) of the Doetinchem Cohort Study in order to be able to extent the analyses on life course effects.

Foreseen follow-up
This project will act as an example project: how can the life course approach improve the understanding of public health in an ageing society, especially in the Netherlands, now and in the future. This will improve our insights in the possibilities of prevention and of the future need for health care services. With the planned further follow-up of the Doetinchem Cohort Study (round 6, years 2013-2016) we want to extent the protocol to pay more attention to the broad range of old age health problems like tests for eye sight, hearing, walking speed, etc and to measure more intensely the promising life course elements. With this ahead, this project can act as a start of new long-term research theme within the National Institute for Public Health and the Environment. If successful, this can be incorporated in future assignments of the Ministry of Health, Welfare and Sport.

Title:	**Healthy vascular ageing (the impact of lifestyle on diabetes, cardiovascular and kidney diseases and cognitive decline: a life course approach)**
Project number:	**S/260236**
Project leader:	Dr. Ir. W.M.M. Verschuren (Monique) (V&Z-PZO)
Start:	01-06-2011
End:	01-06-2015
Total SOR-budget:	€ 953,600

Motivation

For the Netherlands it is estimated that in the year 2025, one in every five persons will be 65 years or older. With respect to public health, diseases of old age will become more dominant. Knowledge on the impact of modifiable risk factors, and insight into factors contributing to healthy ageing is of great importance. The recent Dutch Health Status and Forecast showed that cardiovascular diseases, diabetes and dementia are in the top-10 list of diseases that have the largest impact on both mortality as well as on disease burden (disability-adjusted life years, DALYs), and their prevalence will strongly increase in the near future. From a public health perspective, it is therefore extremely important to increase the knowledge on the modifiable determinants for these diseases and the impact that can be expected from preventive measures. Therefore, this proposal focuses on the cluster of diabetes, cardiovascular diseases and kidney diseases and on cognitive decline.

Aim of the project

The main focus of this project is on the impact of long-term exposure to combinations of lifestyle and risk factors on the occurrence of chronic (vascular) diseases and cognitive decline. We will answer the following questions:

- What is the impact of (changes in) lifestyle patterns during the life course on intermediate risk factors?
- What is the impact of long-term lifestyle patterns and risk factors on the development of vascular diseases and cognitive decline?
- What can be achieved through a lifelong healthy lifestyle?

Strategic and innovative aspects

The elderly of the future will be different from the elderly of today: newer generations have different exposures at different stages of life, resulting in different risk profiles and different cumulative exposure during their lifetime. For example, elderly men of the future will have accumulated less 'pack years of smoking' but more 'fat years'. The life course approach is a novel way of exploring the impact of risk factors on disease, taking into account the changes over time in risk factor levels and cumulative exposure over a long period. Looking at the impact of combinations of risk factors and diseases is needed to contribute to the multifactor approach to prevention. With respect to cognition, most research is done in elderly populations while we are able to study cognitive function and cognitive decline in a relatively young population. Our strength and unique contribution to the scientific field is that we measure cognition with a set of sensitive tests that enables us to identify subtle changes in cognitive functioning at a relatively young age. Our test battery measures three different aspects of cognition: memory, speed and flexibility, and weighing these different aspects a score we call 'global cognition' is derived. The combination of these sensitive tests with our extensive data on lifestyle fills a blank in the scientific knowledge on cognitive decline. The data of the Doetinchem Cohort Study are particularly suited to use this approach.

Planned activities

Chronic diseases: diabetes, cardiovascular disease and kidney disease. Topics to be studied in this project are:

- Descriptive analyses on the dynamics in lifestyle (smoking, physical activity and dietary patterns) and risk factors (body mass index, blood pressure and lipid levels) over the five research rounds of the Doetinchem Cohort Study.
- Impact of longitudinal changes in lifestyle on one or more risk factors and diseases. Based on the results of the descriptive analyses, a choice will be made for the lifestyle or risk factor that is most dynamic, and study the relation with other risk factors and diseases for that factor.
- Impact of lifelong exposure (e.g. accumulated 'fat-years') on diseases.
- Determinants of healthy ageing by comparison of contrasting groups. For example: lifelong healthy habits vs lifelong unhealthy habits: What are the differences in disease rates? And lifelong healthy risk factor levels vs deteriorating levels with ageing: What are the determinants of stable healthy levels?

Lifestyle determinants of cognitive decline. Topics to be studied in this project are:

- The impact of lifestyle (smoking, alcohol consumption and physical activity) on ten-year cognitive decline. A choice will be made which factor to focus on.
- Cardiovascular risk factors and cognitive decline. Determinants that will be studied: blood pressure/management of blood pressure, obesity, (pre-) diabetes, and medication use (statin, aspirin).
- Differences in cardiovascular characteristics of persons with strong versus mild ten-year cognitive decline will be studied. Special focus will be on the prevalence/incidence of clustering of vascular risk factors (the metabolic syndrome) as determinant of cognitive decline.
- Dietary patterns, computed with factor analyses or based on the literature, will be associated with cognitive function at baseline and with ten-year cognitive decline.
- Special groups: effect modification by ApoE (Apolipoprotein) genotype will be tested for all associations if we are able to raise enough funds to determine ApoE.

Planned products

Products will be:

- Approximately ten scientific peer reviewed papers.
- PhD thesis.
- Fact sheet with the main results of the project, aimed at the policymakers at the Ministry of Health, Welfare and Sport.
- Integration of our results, into the web-based National Public Health Compass and the next Health Status and Forecast document that will be published in 2014.
- Results will be used as input for new versions of the RIVM's Chronic Disease Model in order to improve public health modelling exercises.

Foreseen follow-up

With respect to cognitive decline, the present project will expand our knowledgebase that will assist us to better advise the ministry when – as expected – in the near future dementia will become more prominent on their agenda. In addition, results of the present study may lead to lifestyle recommendations and be used in preventive medicine in order to diminish the risk of cognitive decline and postpone or even prevent the development of dementia. We believe our cognition data are truly unique, and in exploring them further, we will seek additional funding.

This project will deliver quantitative estimates of the impact of lifestyle and metabolic risk factors on chronic diseases. Because we look at combinations of factors, the full impact of a healthy lifestyle becomes apparent. This will give information on the best targets for chronic disease prevention and further strengthen the case for primary prevention through lifestyle changes.
The measurements of blood parameter that define kidney function will enable us to explore this field of research. These measurements, in addition to the wealth of long-term data on risk factors and health, will enable us to obtain additional funding for further research in this field.
The manpower to harvest these data will enable us to seek cooperation with other national and international research groups, to confirm for example our results in another dataset. It will also enable us to keep participating in international networks, especially those that are related to the European EPIC project, to which also the Doetinchem Cohort contributes.

Title:	**Early origins of disease**
Project number:	**S/260306**
Project leader:	Wijga, mw. dr. A.H. (Alet) (V&Z/PZO)
Start:	01-10-2011
End:	31-12-2015
Total SOR-budget:	€ 686.500

Motivation
Healthy ageing starts early in life, even before birth. Children whose mothers were pregnant during the Dutch Famine 1944/5 ("de hongerwinter"), for example, have increased prevalence of diabetes, obesity, cardiovascular and respiratory disease and breast cancer in adulthood.There are even indications for poorer health in the next generation. The chronic diseases that result in decreased quality of life, disability and in premature mortality, mostly become apparent in older age, but they originate from conditions and behaviour much earlier in life. Longitudinal studies that started several decades ago, are now providing us with insights that, for example, high cholesterol levels in adults were determined already in childhood or even before birth and that overweight in children is an important predictor of a range of adult chronic diseases. Health in old age is linked to early life conditions in at least two major ways.

- Early programming*:* The concept of 'fetal programming' or 'Developmental origins of health and disease (DOHaD)' proposes that all organ systems of the child undergo developmental programming in utero or very early after birth, which predetermines the child's physiologic functioning during later life.
- Behaviour*:* Although evidence for the importance of early programming by epigenetic regulation is rapidly accumulating, clearly, this form of programming does not imply predestination. Early programming may determine a 'risk profile' and affect health many decades later, but exposures throughout the life course influence the actual health outcomes. Behaviour is a major determinant of today's most common chronic diseases and from a public health point of view, behaviour and the environmental determinants of behaviour are the most important targets that enable policy makers to influence the health of the population. Although deterioration of health tends to occur in older age, the behavioural factors that precede it, are likely to have been established as early as in childhood or adolescence.

Prenatal and early life exposures have convincingly been linked to disease risk in older adults. Very little is known however about the processes that take place during the decades between the beginning of life and the time when chronic

diseases become manifest. In the Netherlands (like elsewhere) cohort studies are available that follow adults into old age besides birth cohorts that follow children from (before) birth into childhood. Studies that successfully follow children from birth through adolescence into adulthood are scarce.

The PIAMA birth cohort is the first cohort in the Netherlands that is getting close to being able to bridge the gap between insights obtained from birth cohorts and from adult cohorts. The PIAMA study was originally designed to study the early origins and natural history of asthma and allergy and the lifestyle, environmental and genetic factors influencing the development of asthma and allergy. Since lifestyle factors were documented meticulously from prenatal life over the course of childhood and follow-up was very succesful, the scope of the study was extended to a lifecourse study covering other chronic diseases of affluence as well. SOR funding has been granted to collect new questionnaire data from the children and their parents in 2011-2012, when the children will be 14-15 years. This further follow-up of the PIAMA cohort will provide us with essential insights in the development and determinants of health related behaviour of today's adolescents.

Aim of the project

The aim of this project is to investigate the early origins of healthy ageing. Within the project we will develop two specific lines of research.

- We will study the influence of environment and behaviour throughout the period from before birth up to adolescence on cardiometabolic and respiratory biomarkers, including BMI (body mass index), lung function, blood pressure, serum cholesterol and HbA1C.
- We will conduct a nested case-control study within the PIAMA cohort on the association between epigenetic changes and overweight and related metabolic outcomes in 15-16-year-old children.

Strategic and innovative aspects

New and unique data will be used in this project on the development of lifestyle and health in children from birth to adolescence. The PIAMA study is one of the first cohorts in Europe following children from pre-birth into adolescence and in the Netherlands no other studies currently have such data available.
Epigenetics is a highly innovative field of research that is evolving very rapidly. The relative importance of epigenetic modulations with regard to adult disease and therefore their relevance for public health, are still completely unknown however. The partnership in this project between GBO with its research on overweight and the PIAMA researchers in Groningen, who focus on the development of asthma, will give RIVM a strong position in this field. It will also form a basis for further (inter)national partnerships and collaboration in the future.
Innovative statistical techniques for longitudinal data analysis will be applied. Some risk factors have early effects that seem to 'die out' as the children grow older, whereas other factors have no visible effects in the first years of life, but are associated with health at later ages. The PIAMA study was one of the first that was able to show such developments, using advanced statistical methods and several awards were obtained for the results of those analyses.

Planned activities

The project proposed here, involves two main activities:

- Epidemiological analyses on associations between health related behaviour in different periods of life (from pre-birth up to adolescence) and development of chronic diseases.

- Determination of epigenetic profiles in a selection of overweight and normal weight adolescents.

Planned products
- A database containing data from questionnaires completed by ca. 2500 14-year-olds and their parents on a wide range of environmental and lifestyle factors and health.
- Epigenetic profiles of ca. 200 children, which will provide a rich source for further studies on the role of epigenetic changes in the association between early life exposures and the development of chronic diseases.
- Around 20 papers will eventually result from the new data.
- PhD thesis based on 5 papers in peer-reviewed journals.

Foreseen follow-up
Based on past successes in this respect, we expect from this project long term results in the form of new assignments for different RIVM centres, new national and international collaborations and acquisition of funding from other sources. This will include new input for the Centre for Public Health Forecasting (VTV). 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 have been able to provide the Ministry of Health 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. The international position of RIVM will certainly benefit from continued participation in the PIAMA birth cohort. In the international scientific community, birth cohort studies with such a long follow-up and such a wide range of data available are highly valued and PIAMA is a much sought after partner in EU and other international projects.

Title:	**Determinants of social participation in old age**
Project number:	**S/270216**
Project leader:	Dr. P.E.D. Eysink (Petra) (V&Z-VTV)
Start:	01-01-2011
End:	31-12-2013
Total SOR-budget:	€ 395,188

Motivation
As western populations are ageing rapidly, a scarcity in the labour force is foreseen. In 2009 almost 15% of the Dutch population was aged 65 years and over. The prognosis is that the share of elderly in the population will increase to 25% in 2050. New policy plans therefore include a gradual postponement of the retirement age to the age of 67 in 2025. This means that persons will have to work longer. Another consequence of the growing ageing population is an increasing need for informal care. This need cannot be met by the increasingly smaller proportion of younger adults alone. As a consequence, our ageing population has to participate in the labour force longer, has to meet the increasing need for informal care, and – at the same time – has to find time for leisure time activities and voluntary work. Presumably, an increase in one of these types of participation of the elderly goes at the expense of the others.

Many studies have shown that chronic diseases and especially disabilities hamper participation. This is true for paid and voluntary work as well as for different kinds of leisure time participation. At the same time that our society needs the elderly to participate more, society also faces more elderly people with chronic diseases. About forty percent of the people aged 55-64 years have at least one chronic disease, and this percentage increases with age. The prognosis is that this number will grow, not only because of the ageing of the population, also because of epidemiological trends in chronic diseases like trends in risk factors. For example, due to ageing of the Dutch population the number of patients with diabetes will increase with 33% between 2007 and 2025. However, the number of people with diabetes will be even higher in 2025 because the number of people with obesity (one of the main risk factors for diabetes) will also increase during this period.

Healthy ageing is often seen as a strategy to cope with the expected shortages on the labour market and in informal care. The focus generally lies on preventing diseases and disabilities. Since previous research has shown that chronic diseases and disabilities hamper participation in society, preventing disease is one pathway to optimize participation. Another strategy is to facilitate people who already face a chronic disease or disability to participate. Until now, knowledge about factors that influence different types of participation is fragmented. As a result, it is difficult to pinpoint what factors determine participation, for whom and in what circumstances. There are clues that this depends not only on chronic diseases and disability, but also on factors related to the social and physical environment, health care and psychosocial determinants. To know the contribution of these determinants can be useful for policymakers to create better opportunities for participation of the elderly. It cuts both ways: creating opportunities for participation enhances the quality of life of the elderly and it can, to some extent, alleviate the expected shortages on the labour market, in voluntary work and in informal care.

Aim of the project

Our aim is to find explanations for the fact that some elderly participate in paid work, voluntary work, informal care, and leisure time activities, whereas others do not. What is the relative weight of disease-related factors, health care, life style factors, environmental factors and psychosocial factors? How do these interact? Do these apply to the whole research population or just a part of it? Does participation in one domain go at the expense of other domains? To answer these questions, we will study people aged 55 years and over because this way we can measure all types of participation, including labour participation. Specific objectives are:

- To make a theoretical framework of the determinants that influence social participation in the elderly, including causality and possible interactions between these explanatory factors.
- To quantify the contributions of the different determinants for the Dutch situation, by investigating the relations put forward in the theoretical framework for the total elderly population,- for elderly with and without chronic diseases or disabilities and for elderly in different socio-demographic groups.

Strategic and innovative aspects

Our research will add to the knowledge on how to optimize participation of the elderly. New in our approach is that we investigate different domains of participation (paid work, voluntary work, informal care, leisure time activities) in connection to each other and that we will look at a broad range of determinants:

health, life style, health care, psychosocial factors, and the social and physical environment. Moreover, we will study the socioeconomic inequality in these associations, which may reflect the need for differential interventions. Our focus on the relation between health and contributions to society will contribute to new insights on the 'health is wealth' and 'healthy ageing' principles. Furthermore, this project enhances the strong position the centre for Public Health Status and Forecast of the RIVM has on bringing together information and expertise. Doing this on a relatively new subject, adds to this strategic position, also in an international context.

Planned activities

- Building a theoretical framework of the determinants that influence social participation in the elderly.
- Hypotheses based on the framework will be studied for the Dutch situation, by analysing explanatory factors for social participation of the elderly in the Dutch situation in four relevant and available Dutch data sources.

Relationships between all available and relevant explanatory factors and the four types of participation in each of the four data sources will be analysed in a similar way. We will use (logistic) regression or other multivariate models to quantify the effects and interactions of the determinants on social participation.

Planned products

- Three or four articles that will be published in international peer reviewed journals.
- The information will also be used in the Public Health Forecast 2014 and other products of the centre of Public Health and Forecasting, such as the National Public Health Compass.

Foreseen follow-up

The results of this project will undoubtedly find their way to the next 'Public Health Status and Forecast' in 2014, as a new step in the already available work on societal benefits of health. Since this topic is also on the agenda of the policymakers, both at the Ministry of Health, Welfare and Sport (VWS) and at the Ministry of Social Affairs and Employment (SZW), it is important for the RIVM to keep up to date. In coming years, this may lead to new assignments from both ministries.

Title:	**Monitoring human ageing**
Project number:	**S/340005**
Project leader:	Dr. M.E.T. Dollé (Martijn) (VGC-GBO)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 1,428,348

Motivation

Life expectancy of the Dutch population has increased significantly, like in most developed countries. Moreover, the mean population age increases due to the baby boom generation reaching old age. As a result there will be a progressive increase in the proportion of elderly and concomitantly a higher prevalence of ageing-associated diseases, like type 2 diabetes, cardiovascular disease and cancer, with a high impact on affected individuals and high costs for society. However, both human and animal studies have shown that healthy ageing, i.e. longevity accompanied by relatively mild ageing-associated pathology, is

possible. The only currently known reproducible intervention strategy to stimulate healthy ageing is dietary restriction (DR), i.e. reduced food intake without malnutrition. In several organisms, including rodents, and more recently primates it has been shown that various forms of DR cause a remarkable increase in lifespan and decrease of ageing-associated pathology. DR activates an intriguing adaptive response leading to decreased metabolism, protein synthesis and growth. Though long term DR is not a feasible intervention in humans, short term DR is. Short term DR in mice increases stress resistance, leads to better survival and recovery after surgery, and produces an adaptive response resembling that of long term DR.
Our working hypothesis is that variation in ageing is influenced by differences in endogenous metabolic profiles. Hence, ageing-associated diseases could be modulated through regulation of these metabolic processes, e.g. by mimicking a DR induced adaptive response. Compared to healthy individuals in the normal population, severely obese individuals age unhealthy. Obesity is an important risk factor for several metabolic and ageing-related conditions such as type 2 diabetes, cardiovascular disease and early mortality, and has therefore been suggested to represent a form of accelerated ageing. In this respect healthy normal weight and obese individuals appear suitable cohorts to further analyse the presence and extent of the adaptive response.

Aim of the project
The overall aim of this project is to identify targets and markers for novel intervention strategies to prevent ageing-associated diseases and to promote healthy ageing. To this end we will pursue three specific objectives:

- Determine signatures of the adaptive response in healthy and unhealthy individuals.
- Identify biomarkers that act as indicators for the extent of the adaptive response, monitor biological age, and/or specify health status.
- Evaluate longitudinal development of identified biomarkers in the prospective Doetinchem population as predictors of ageing-associated disorders and indicators of successful intervention.

Strategic and innovative aspects
Our experience in marine studies has provided us with a sound scientific basis on ageing. The current project is explicitly aimed at translating the results obtained from these animal studies to human health and in this manner valorise investments made before. The current proposal offers us the availability of exceptional human samples: serum from genetically predisposed long-lived individuals and serum and internal organs from the normal healthy population and unhealthy (obese) individuals in which the adaptive response to DR can be measured. This provides us with a unique opportunity for optimal human-mouse comparison and human-based research to develop interventions and monitoring tools to prevent ageing-associated pathology and support healthy ageing. Past investments made in the rather exclusive longitudinal setup of the Doetinchem Cohort will now be (additionally) substantiated by evaluating the uncovered biomarkers, their predictive value for ageing-related ailments, and possibly intervention strategies.
Furthermore, this project integrates the fundamental knowledge from universities and the applied controlled testing in human clinical settings with epidemiological research on an international scale. This multidisciplinary approach exceeds the potential of any single entity, and extends the network and knowledge base that is essential for the RIVM to keep providing sound health advice.

Here we propose to develop tools to monitor human aging and intervention strategies to optimize future investments in public health and provide evidence-based solutions for the economical and societal problems of the ageing society that is approaching.
The focus on differential metabolic profiles will provide valuable insight relating to specific sensitivities of the elderly, e.g. toxicological and pharmacological sensitivity.
Last but not least, a major additional benefit from the proposed collaboration in the proposed project is the opportunity to contribute to and gain knowledge of improved surgical efficacy and recovery. This benefit translates to enhanced well-being of surgical patients and reduced health care costs.

Planned activities

- Tissue biopsies and minimally invasive sample material (e.g. blood, saliva, urine) from both mouse and human origin will be collected from diet restricted individuals and ad lib controls. The collected biomaterials will be analysed for RNA expression and proteome or metabolite changes resulting from the diet restriction induced adaptive response. Markers characterizing the adaptive response and potential biomarkers to monitor the ageing process will be extracted from the acquired data sets.
- Simultaneously, we will provide a literature overview of the state of the art of biomarkers of ageing based on different types of human material that can easily be assessed in large-scale population-based studies. We will include the developments and findings in European (EU)-projects like MARK-AGE (study to establish biomarkers of human ageing) n this overview.
- We will apply the Doetinchem Cohort to evaluate biomarkers as predictors of ageing and associated disease both on an individual and a population level.

Planned products

- Dutch knowledge sheet with a layman description of the state of the art of biomarkers of ageing and its perspective for public health.
- Development of a biomarker assessment protocol for the Doetinchem Cohort and possibly amended guidelines for human sampling and storage conditions for optimal functional biomarker assessment.
- New collaborations (e.g. clinical setting Erasmus MC).
- Human biomarkers to monitor aging, disease and interventions.
- Improved preoperative diet guidelines to limit surgical trauma and enhance post operative recovery.
- Advice on products aimed at healthy ageing by mimicking DR, such as resveratrol, rapamycin and derivatives, which will be marketed. This is a new class of foreseen anti ageing drugs with unpredictable long term outcome.
- Peer reviewed publications.
- PhD thesis.

Foreseen follow-up

Our results may feed future research eventually leading to intervention strategies and health monitoring during aging. In particular health markers would be highly desirable tools as early indicators to select the most efficient interventions with a positive outcome on public health, and thus help to maximize the efficiency of governmental investments aimed at decreasing disease burden in the general population; a relevant topic regarding the demographic developments in the Netherlands.
As a secondary spin-off, this project might contribute to perioperative interventions to improve patient recovery time after surgery with a positive outcome for health care, both for the patient and from a financial point of view.

Title:	**Are supplements good for healthy ageing?**
Project number:	**S/340006**
Project leader:	Dr. ir. E.H.J.M. Jansen (Eugene) (VGC-GBO)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 847,800

Motivation

Supplementation of antioxidants and vitamins to our daily food is marketed as being beneficial. These supplements are broadly available and intake is less controlled and possibly not as beneficial as providers want us to believe. This is enforced by the recent evaluation of health claims by the European Food Safety Authority (EFSA). According to EFSA 'claims made on the antioxidant capacity/content or properties of food/food constituents based on their capability of scavenging free radicals *in vitro* refer to a property of the food/food constituent measured in model systems, and that the information provided does not establish that this capability exerts a beneficial physiological effect in humans'. In a recent food consumption survey in 2007/2008 of the Dutch elderly population (51-69 years of age), vitamin and/or mineral supplements were consumed on a regular basis by 36% of the participants. Most of the supplements used were a single or multicomponent supplement containing antioxidant vitamins. Since oxidative stress is one of the key inducers of ageing-related diseases, the majority of available supplements are directed to maintain a proper antioxidant balance. However, the use of high doses of single antioxidants, which are still widely available in the Netherlands, may result in an adverse pro-oxidant effect.

The benefit of supplements in humans is questioned in many studies. For instance, in a recent Cochrane review an increased mortality was found in a number of intervention studies in which selected single antioxidant vitamins were used**.** In these studies ageing was not considered as important issue. Our own studies in wild type mice also showed that chronic lifetime exposures to antioxidants resulted in liver toxicity. However, to mice lacking antioxidant defence mechanisms supplementation with anti-oxidants appeared to be beneficial to some extent. Again this clearly links oxidants and their defence systems to healthy ageing.

Based on our own observations and literature data we hypothesize that owing to the fact that genes or their known variants have been selected for their beneficial contribution during the reproductive period, these same genes might have a negative net effect on the ageing process thereafter (Pleiotrophic gene hypothesis). If so, intervention strategies with supplements should be adapted to the different phases in life, or should only be applied at the optimal, older age period.

Aim of the project

Our specific aim for this project proposal is to test the hypothesis that supplementation of antioxidant vitamins in humans have positive health effects only in later stages of adult life by counteracting the detrimental effects associated with ageing. In the reproductive stage of life antioxidant supplement use is of no additional value and can even be harmful.

Specific objectives are:

- To perform with a multivitamin and mineral supplement a lifetime intervention study in mice, starting at different ages, to investigate differences in possible adverse or beneficial health effects.
- To perform with a the same multivitamin and mineral supplement a short intervention study in humans of two different age groups, to investigate a

possible change in a set of the same biomarkers as in the abovementioned objective.
- To examine in human cohorts the health impact of antioxidant supplements at different ages in (inter)national age-related human cohorts (project CHANCES, etc.) by measuring the serum levels of a final set of biomarkers in these studies.
- To report our findings in international literature and make an advisory report to the regulatory authorities for follow-up initiatives.

Strategic and innovative aspects

This project is innovative in the fact that it translates knowledge gathered from animal studies to human cohort studies. This knowledge will now be adapted to age-related human cohort studies such as the EU's 7th Framework Programme (FP7) project CHANCES. In CHANCES suitable cohorts will be selected which have sufficient individuals with supplement use to participate in this project and to test our hypotheses. In these activities also differences between men and women will be subject of study.

A combined expertise from our international networks and existing knowledge of ageing processes in mice, oxidative stress processes, redox-related studies and the application to human longevity cohorts makes this approach new and innovative. Our findings and combined expertise within RIVM will supply a scientific base for future political decision-makers with regard to supplement use and availability in the Netherlands.

Planned activities

- Selection of supplement composition.
- Selection of initial biomarkers.
- Mouse experiment.
- Human intervention study.
- Selection of final biomarkers (after eventual positive go/no-go decision).
- Selection of samples from human cohorts (after eventual positive go/no-go decision).
- Analysis, conclusion and reports.

The results of all studies will be analysed with statistical methods used in epidemiological research. Conclusions will be drawn concerning the beneficial or detrimental effect of the use of multivitamin supplements for different age groups.

Planned products

- This project will provide a recommendation for save use of supplements. Should this project indicate that consumption of certain vitamins and supplements may pose an actual health concern at all or certain ages, more restricted advises to change policy of supplementation should be given by responsible authorities.
- A better understanding of the association between (antioxidant) vitamin status and changes in parameters of redox status, disease states and longevity. As a result of this project, a well-defined set of biomarkers will be developed, which can be used in future intervention studies.
- Peer reviewed international journals.

Foreseen follow-up

The results of this project can be used in many public health areas, if the hypothesis of this project will be proven. Then the following follow-up activities can be initiated.

With the results of this project the RIVM can fulfil one of its main tasks by signalling future developments in public health issues of both young adults and

elderly. Additional projects can be formulated and imbedded in regular Governmental programmes. In addition RIVM can extend the coordination and cooperation in international European Commission (EC) programmes. Also the Ministries of Public Health (VWS) and Agriculture (VWA) can use these results to a better defined policy of the use of supplements. Both Ministries can play a more substantial role in the policymaking within the Europe.

Title:	**Fetal origin of adult disease**
Project number:	**S/340007**
Project leader:	Dr. L.T.M. van der Ven (Leo) (VGC-GBO)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 505,698

Motivation

Ageing related diseases are a growing problem in the Dutch population, as they are in the Western world. More than two chronic diseases are observed in over 60% of people aged 65-75 and in 85% of people aged over 85. Cardiovascular diseases, osteoarthrosis, obesity, diabetes, malignancies and depression are observed as a single disease or in combinations, at higher age also with dementia. Apart from managing the care, an important line of research considers prevention of these diseases, which is mostly targeted at well-known risk factors such as life style and diet.

In addition to this, the hypothesis has recently been put forward that health and disease at later age are influenced by factors early in life. Thus, exposure early in life to environmental stressors, such as contaminants, maternal diet and life style, may be associated with changed longevity and with ageing related diseases (healthy ageing). This hypothesis is based on epidemiological observations, as in the Dutch hunger winter cohort, in which individuals who experienced the hunger conditions as a foetus, showed an increased prevalence of various ageing-related metabolic diseases. Another example can be found in Holocaust survivors, who show an inverse relation between the age at which the Holocaust was experienced and cancer incidence at later age. This concept of perinatal programming is known as Developmental Origin of Health and Disease (DOHaD) and a putative mechanism is a changed gene expression due to non-mutational changes to the genome, the so-called epigenetic modifications. These include changes of methylation of DNA and acetylation of histones.

As may be concluded from the examples above, prenatal programming in humans may result from (maternal) under nutrition early in life, and lead to metabolic diseases such as obesity and diabetes, and also to development of cancer. However, other factors have also been implicated, e.g. maternal over consumption of folic acid resulting in overweight of the child, and prenatal exposure to pesticides as a programming factor related to brain dysfunction, particularly learning disabilities. Supporting evidence for the concept of prenatal programming comes from animal studies, showing programming effects of environmental contaminants for obesity.

In view of the widespread consequences, the concept may be highly relevant for public health and justifies initiatives to explore this field. For, should this concept be true, it will provide leads to develop policy for improved protection of the developing human being, i.e. protect the foetus and the young child from exposure to compounds which may affect the epigenome.

Aim of the project
The key hypothesis in the project is that a relatively stable epigenetic profile that is generated early in life determines health and disease later in life. Therefore, the aim of this project is to build expertise to advise national and international governmental bodies regarding improved prenatal hygiene, i.e. protection of the highly susceptible developing human individual against adverse influences (environmental contaminants, maternal dietary factors) for which until now, no accurate tests are available. To build this expertise, we will need to improve our understanding of the role of perinatal factors in the onset of ageing-related disease.
The first objective is to expand our ongoing studies towards this aim:

- The ongoing epidemiological and animal studies in OBELIX (Obesogenic endocrine disrupting chemicals: inking prenatal exposure to the development of obesity later in life,European Commission funded project), which are targeted at analysis of effects on obesity/overweight, will be expanded towards further metabolic analyses.
- Materials from an ongoing obesity case-control study, derived from the Rotterdam dietary restriction study, will be used to verify the relevance for humans of DNA methylation changes which in the OBELIX animal studies are causally linked to obesity.

The second objective is to build a scientific network focusing on early life programming of ageing related disease. Such a network will provide further input on the subject and improve assessment of the relevance of new data in the field.

Strategic and innovative aspects
Although identified as an issue in the EU's 7th Framework Programme (FP7), early life programming is, until now, not recognized as an important aetiological factor of chronic diseases of the old age. At the current state of the science it is not possible to estimate the importance of this mechanism in the complex of aetiologies. Through combination of existing data and new research, this project will provide more insight in the relative contribution of early life factors and thus bridge science with policy. This proposal specifically addresses the link between early life environment and the condition at old age. The analysis of specific underlying molecular mechanisms to explain this link are important to propose new prevention and intervention strategies of ageing related disease, respectively early in life and at adult age.

Planned activities
The project will elaborate on both human and animal materials generated in two other projects. Activities are:

- Development of epigenetic tools.
- Animal studies, including measurement of metabolism related parameters.
- Evaluation of OBELIX results.
- Mother-child studies, including measurement of metabolism related parameters.
- Evaluation of OBELIX results.
- Epigenetic analysis in Rotterdam Dietary Restriction Study.
- Final evaluation and reporting.

Planned products

- Contribute to the assessment of the validity of the concept of developmental origins of health and disease, by critical appraisal of new reports in the field and also by providing supportive or rejective evidence.
- Expertise to advise on protection of a particular susceptible group, i.e. the developing human being, against early life influences which may affect health later in life.

- Approximately five peer reviewed papers.
- PhD thesis.

Foreseen follow-up

This project is intended to provide evidence for the hypothesis of determination during early life of chronic disease at old age, and thus should emphasize the importance of decisions early in life to prevent chronic disease at old age. Elucidation of the underlying epigenetic mechanism of this principle may provide a lead to design an intervention strategy (focusing on prevention of the phenotype).
Beyond this, the project will provide RIVM a position to align with ongoing international initiatives, such as the International humane epigenome consortium. The expertise which will be generated through this project will make RIVM a competitive partner in new initiatives in the field.
This project will generate follow-up questions, regarding further substantiation of the importance of underlying epigenetic mechanisms relative to other aetiological factors, such as life style during adult life. Further follow-up questions may address preventive strategies (prenatal/early life hygiene), and intervention at adulthood.

Title:	**Cofinancing for CHANCES**
Project number:	**E/340032**
Project leader:	Jansen, dhr. dr. ir. E.H.J.M. (Eugene) (VGC/ GBO)
Start:	01-01-2012
End:	31-12-2014
Total SOR-budget:	€ 228.400

Motivation
The CHANCES project aims at combining and integrating on-going cohort studies in order to produce evidence on ageing-related health characteristics and determinants in Europe, and their socio-economic implications. Thirteen cohorts participate in the project, covering populations from 18 EU Member States, four associate countries, and three additional countries. The combination of these different studies would lead to an integrated approach to the study of health in the elderly. Additionally, the study will generate a unique resource for additional studies on health and its determinants in the elderly. Provisions will be made to allow for this work to be extended.

Aim of the project
The CHANCES project aims at combining and integrating on-going studies in order to produce evidence on ageing-related health characteristics and determinants in Europe. Thirteen cohorts are included in the project.

Strategic and innovative aspects
The aim of WP9 is to identify a set of biomarkers that can act as a general predictor of health in the elderly, and which correlates with absence or presence of various age-related chronic diseases, such as cancer, diabetes and CVD, osteoporosis, cognition and total mortality, studied in WP3 to WP7. It is plausible that a particular biomarker (e.g. total antioxidant capacity) is identified

as predictor of health in the elderly, allowing the emergence of an important intermediate factor in the chain of events linking risk factors to health.

Planned activities

- To make an inventory of the already measured biomarkers in the contributing cohorts (Tasks 1).
- To select an additional set of biomarkers which is predicted to correlate with more multiple endpoints or age-related chronic disease (Task 2) .
- To make a selection of the number of samples and the identification of the samples in each cohort to be measured (Task 2).
- To measure the selected biomarkers in the selected samples (Task 3 and 4).
- To list the results in a database for the project leaders of WPs 3 to7 and 9 (Task 5).

D.1: Month 14 An inventory report of the participating cohorts including the previously measured biomarkers and availability of samples for additional measurements.
D.2: Month 26 A planning report for the measurements of additional biomarkers in the various cohorts including sample number and identity.
D.3: Month 40 Report of the measurements of additional biomarkers per cohort (as an excel file), including methods and quality control.

Planned products

- Task 1 (month 1-12): To make an inventory of the already measured biomarkers in the contributing cohorts. The responsible persons of all participating cohorts will be contacted for information of the characteristics of the cohorts. In addition information on the blood samples will be obtained regarding sample availability, storage conditions, etc.
- Task 2 (month 6-18): To plan the measurements of a new set of biomarkers in the various cohorts in cooperation with the WP leaders of WP 3-7 and 9.
- Task 3 (month 12-24): To collect the selected samples from the biobanks of the cohorts together with a working list with sample identification numbers. The collection of the samples in the cohort will be done by the responsible persons of the particular cohorts. Transport will be arranged under freezing conditions (dry-ice) to the laboratory facilities of RIVM in Bilthoven, the Netherlands.
- Task 4 (month 24-36): To measure the selected parameters in the samples by different techniques. Measurements will be performed with different techniques by experienced technicians. The data will be listed in an excel database.
- Task 5 (month 36-60): To supply the results of the biomarker measuremenst to the WP leaders of WP 3 to 7 and 9. The results of the biomarker measurements (as an excel file) will be send to the WP leaders of interest. Also the methods will be reported and the quality control data. Support will be given for methodological questions.

Foreseen follow-up

The results of this project can be used in many public health areas of aging. With the results of this project the RIVM can fulfill one of its main tasks by signaling future developments in public health issues of adults and elderly. Additional projects can be formulated and imbedded in regular Governmental programs. In addition RIVM can extend the coordination and cooperation in international (EC) programs because of the international network of cohorts and Institutes involved in CHANCES.

Title:	**DNA repair, mutations and cellular aging**
Project number:	**E/340100/01/SO**
Project leader:	Dollé, dhr. dr. M.E.T. (Martijn) (VGC/ GBO)
Start:	01-01-2011
End:	31-3-2014
Total SOR-budget:	€ 273.693

Motivation

In comparative studies with mutant mouse strains can have dramatic effects on the outcome of survival studies, e.g. variations in genetic background, environmental conditions and nutritional status as well as animal handling and tissue processing. In order to bring mutant mouse strains described in this program in the same genetic background, a centralized animal facility to house the jointly used mutant mouse strains was considered essential to this program, even though the different investigators participating in this program are located in different institutions. The RIVM Animal Facilities (animal/pathology core Institute) are extremely well equipped to conduct long-term animal studies.
To ensure uniformity and viability all subsequent cohort studies will be conducted in a defined FVB-C58BL/6J F1 background. Since all mutant mouse strains will be kept and monitored in the same core unit (together with the new standard FVBC57BL/6J F1 strain), different aspects of early senescence are better recognized by comparing data obtained from individual studies performed at different locations, all using different historical backgrounds.
The Laboratory for Health Protection Research is an established and acknowledged centre of excellence in the field of genetic toxicology, chemical carcinogenesis and pathology. Over the last eight years the Animal/Pathology core unit has successfully conducted several longevity and cross sectional studies with mice having a defect in DNA repair and/or RNA transcription. Some of these mouse strains showed phenotypes of accelerated aging. As part of the present program renewal application, the animal and pathology core will continue to conduct such studies, but will now have a more specific focus (based on the results obtained in the previous grant period) and will include intervention studies. On the basis of anticipated results of the 5 projects, intervention strategies will be developed in our mouse models, e.g. to eradicate senescent cells and to ameliorate ageing phenotypes through pharmaceutical and/or nutraceutical interventions.

Aim of the project

Overall, the specific aims of the animal/pathology core are:

- To ensure uniformity and homogeneity of animals and the environment in which the animals will be housed; consequently the animals will be backcrossed into the same genetic C57BL/6JxFVB F1 hybrid background.
- To ensure that the animals are raised in a pathogen free environment.
- To facilitate the sharing of animals, tissues and cells among the individual investigators.
- To conduct longevity and/or cross sectional studies with various single and double mutant or transgenic mouse models of interest to the consortium (all projects).
- To conduct life-span intervention studies with short-lived progeroid mouse models, with one or two added cross sectional studies for the most promising interventions in mutant and wild type mice (Projects 1 and 3).
- To conduct full histopathology on all animals from the longevity studies and if necessary also on mice from the cross sectional studies.

Strategic and innovative aspects
The consortium involved in the NIH/NIA program project has been producing fundamental insight in the aging process for the past 12 years, as recognized by the awarded 3rd consecutive 5 year funding period. Next to first hand access to state of the art aging research, participation in this consortium provides an international network. Furthermore, in this current funding period the research is no longer limited to mouse models and human and murine cell cultures, but includes human longevity cohorts to translate the findings made model systems.

Planned activities
21 Cohorts with a lifespan from 0,5 to 2 years.

Planned products
- Peer reviewed publications.
- Scientific presentations (oral and posters)
- Extended networks
- Advice on products and life-style recommendations aimed at healthy ageing

Foreseen follow-up
In general better insights in the molecular mechanisms behind the aging process are expected. In time turn this should lead intervention strategies to promote healthy aging and biomarkers to qualify the individual aging process. Moreover, the mouse models under study may appear suitable as short term test models for aging intervention strategies, such as diet modifications or specific molecules/drugs, modulating e.g. the redox balance or mimicking caloric restricted diets. The gained knowledge should facilitate governmental health recommendations and interventions to reduce disease burden associated with aging in the general population.

Title:	**Biomarker associated dietary patterns for improving health of the elderly?**
Project number:	**S/350050**
Project leader:	Boer, mw. dr. ir. J.M.A. (Jolanda) (VGC/CVG)
Start:	01-01-2012
End:	31-12-2015
Total SOR-budget:	€ 780.000

Motivation
The proportional increase of the ageing population is associated with an increase in chronic and degenerative diseases and a declining potential of services on the labor market. This, together with the increasing costs and pressure on health services are taken up as 'the' challenge for the next decades. Indeed, the baby-boomers are starting to retire now and forces are to be combined in order to keep the valuable experiences and skills of this group for the labor market and societal participation at least a little longer. Among the key determinants of influence on the eventual health status, physical functioning and quality of life of people are dietary intake and nutritional status. In older persons inadequate nutritional intake is highly prevalent and an important cause for declining functionality and other health effects. A focus on dietary intake is important, as food intake is a main determinant of lifestyle and an integral part of well-being determining quality of life. Also, food intake interventions may be worthwhile to pursue, as well as feasible to introduce in every stage of the life cycle, even in

the oldest people. Because they are very vulnerable, several important target groups for preventive interventions can be notified: seniors aged 75 years and over, single elderly women, elderly people with a low social economic status, ethnic groups of seniors and those elderly who need to care for a spouse or other relatives.

Aim of the project

This project aims to derive dietary patterns using health-related biomarkers among Dutch seniors to better describe, predict and quantify public health outcomes of whole diets relevant for the Dutch population. The project will further develop novel methods for the determination of dose-response relationships based on prediction equations from data on dietary patterns and biomarkers characterized by multiple elements. The project will also prepare for the quantification of the net health impact of hypothesized and feasible future dietary pattern changes in seniors.
Specific objectives are:

- To obtain state-of-the-art information and an overview of data on biomarkers and dietary patterns in Dutch seniors and to identify knowledge gaps;
- To identify clusters of health-related biomarkers and associated dietary patterns predicting health outcomes from available data;
- To define healthy vs. unhealthy biomarker profiles and associated dietary patterns and to describe the population segments behind those profiles;
- To construct dose-response relationships between the most relevant dietary patterns and health outcomes based on novel techniques;
- To quantify the net impact on health and quality of life of the most relevant dietary patterns extracted andhypothesized changes in these dietary patterns
- Addressing specific target groups for preventive interventions.

Strategic and innovative aspects

The uniqueness and innovative aspect of this project is the inventory and collaboration on finding those biomarker clusters and the associated dietary patterns that are most relevant for health and subsequent construction of dose-response relationships. There are already some activities and projects on dietary patterns and specific health outcomes, but we will focus on those patterns that are to be associated with biomarker clusters that will explain most variation in (intermediate) health outcomes and that have the largest impact on integrated health measures within our cohorts. The characterization of people with healthy vs. unhealthy dietary patterns should help in tailoring the public health policy. Also the step of dose-response modelling and the subsequent modelling effort to quantify the results of hypothesized changes in dietary patterns in specific ageing groups on the population level is RIVM's niche and is innovative: in the past such quantification was carried out only through interventions on single risk factors. In this project we will develop ways to quantify the influence of changes in a whole dietary pattern. In the nutrition and health field it is increasingly important to integrate research results, regarding lifestyle, in order to grab the general picture on public health and to pinpoint the most important challenges. Dose-response modelling with a public health perspective in the field of nutrition is still in it's infancy, but is increasingly recognized as an important future step. It is vital for RIVM to present its activities on the elderly topic and to show the utilization of its knowledge, including the presentation of our unique modelling expertise in order to attract future commissioners. Furthermore it is important to construct, extend and maintain our nutritional network in this field and to keep up with the external topics and activities.

Planned activities

The project is scheduled as follows:

- Task 1, Month 1-6, Construction of an overview of available cohort and monitoring studies in the elderly focusing on biomarkers as early disease markers in relation to dietary patterns on the one side and health outcomes on the other side. The installation of the expert scientific advisory committee (SAC) will be organized.
- Task 2, Month 6-30, Identification of biomarker-clusters associated with dietary patterns, using algorithmic prediction modeling (e.g. random forest, vector support machines) in available databases.
- Task 3, Month 22-36, Ranking the study population in our database from identified healthy to unhealthy biomarker profiles, using the predictive model and the relations between biomarker clusters and underlying dietary patterns from Task 2.
- Task 4, Month 30–40, Using national food consumption data on the free-living elderly in the Netherlands (n>700), the nutritional quality of the various dietary patterns in the Dutch elderly population as compared to guidelines for a healthy diet will be described, as well as the prevalence in which the dietary patterns occur in 2010/2011 and the characteristics of the Dutch seniors having healthy or unhealthy dietary patterns.
- Task 5, Month 36-48, Definition of the reference dietary pattern scenario and the alternative scenarios. Calculation and quantification of the net health impact in the population based on these scenarios and/or selected target groups for preventive interventions.
- Task 6, Month 40-48. Organization of a workshop for our collaborating colleagues, stakeholders, and our future commissioners. Results accompanied with recommendations will be presented at VWS, EL&I and VWA. Integration of available results in the VTV-2014.

Planned products

(At least) five peer reviewed scientific papers (forming the basis of a PhD thesis).

Foreseen follow-up

Our approaches may retrieve valuable information for future nutrition policies or future consumer education programs initiated by e.g. the Netherlands Nutrition Centre. The information will have impact on the national health policy as defined by the Ministry of Health, Welfare and Sports but also on local health policies. Intermediary organizations for the elderly as the community health services, home-care and meals-on-wheels organizations, Vilans Knowledge Centre on Ageing (formally NIZW), NIGZ 'Ouderen en Gezondheid' may be attracted to our approach to quantify health outcomes of different dietary patterns and will be informed through the fact sheet and workshop. We expect that our increased knowledge will be materialized through new assignments by the Ministry of Health, Welfare and Sports or by EU projects. Also other specific funding agencies (either governmental or non-governmental) may act upon our directions for the future. Finally, we hope that our project will be an overture for a future 'RIVM Healthy Ageing Knowledge Centre'.

Title:	**Adequate medication use by elderly outpatients**
Project number:	**S/370002**
Project leader:	Drs. D.A. van Riet - Nales (Diana) (VGC-KCF)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 447,800

Motivation

The number of elderly people (≥ 65 years) in the European Union is expected to grow from around 84 million (17% of the total population) in 2008 to around 141 million (30% of the total population) by 2050. People's life expectancy is also increasing. These additional life years are likely to go hand in hand with an increased number of diseases i.e. multimorbidity and an extensive use of medicines i.e. poly-pharmacy. The use of medicines by elderly people is almost a factor of three higher to that of the non-elderly. Elderly people living in the Netherlands are using over 40% of the prescription medicines. The total use of medicines by elderly will have increased by approximately 60% in 2035.

Pharmaceutical therapy by elderly patients significantly differs from pharmaceutical therapy by adults as elderly generally take more medicines (i.e. poly-pharmacy), often have multiple chronic illnesses (i.e. multimorbidity) and, therefore, have complex medication regimens. Besides, pharmaceutical therapy by elderly people is complicated by ageing-associated factors, including physiologic changes (decreased renal and hepatic clearance of medicines), a reduction in physical skills (e.g. vision, hearing, manual dexterity and strength) and a reduction in social and cognitive skills (e.g. Alzheimer). In addition, the elderly may be faced with poor health literacy i.e. the ability to access, read, understand and use health care which is necessary in order to make decisions and follow instructions for treatment.

As a consequence, medication self-management (the ability to self-administer a medication regimen as prescribed) is often problematic in the elderly. Therefore, elderly patients are more vulnerable to non-compliant behaviour to pharmaceutical therapy as younger patients. However, most medicines that are currently used by elderly people have not been tailored for use in this vulnerable patient group. Current incentives to improve pharmacotherapy in the elderly mainly focus on physiologic changes of ageing by addressing correct dosing, drug interactions of medicines in the case of poly-pharmacy, adverse reactions and on how to conduct clinical trials in this age group. Little attention has been paid to the special needs of the elderly with respect to the pharmaceutical design of the medicine including the suitability of the user information. The aforementioned underlines the need to investigate the cross-relationship between the pharmaceutical design aspects of medicines for human use including the user information when used in elderly outpatients, medication self-management, compliance and the cognitive, physical and social characteristics of the elderly patient.

Aim of the project

The aim of this PhD study is to investigate the influence of the pharmaceutical design of medicines on medication self-management and (non)-compliance by elderly outpatients, including the relationship between these aspects and the physical, social and cognitive skills of this patient group. Medication compliance is defined as the intended use of medicines. Medication non-compliance, both intentional and unintentional, is defined as not filling a prescription initially, not

having the prescription refilled, omitting doses, taking the wrong dose, stopping a medication without the consultation or advice, taking medication incorrectly, taking medication at the wrong time, or taking someone else's medication.

Strategic and innovative aspects
Improvement of medication self-management and treatment compliance is especially important for elderly patients as they are more likely to be non-compliant to pharmaceutical therapy. Medication compliance is a contributing factor to maintaining patients' autonomy and independence, and non-compliance imposes a considerable financial burden upon the health care system. More than 10% of older adult hospital admissions may be due to non-compliance with medication regimens. Nearly one-fourth of nursing home admissions may be due to older persons' inability to self-administer medications. As the proportion of elderly people in society rises it becomes increasingly important to ensure that their special needs are taken into consideration when developing and using medicines.

This study will affirm RIVM's position as an international knowledge centre on the chemical pharmaceutical quality of medicines for human use, also in special patient groups.

This project will further fit into RIVM's recently started international project on health literacy. Individual responsibility for health and self-management of diseases are promoted and relied on in modern society. In order to prevent health inequality, it is essential to study to what extent patients are capable of taking on this responsibility, and to look for effective ways of stimulating those patients that fail. Health literacy is an emerging topic in European public health research. Putting the concept of health literacy into practice in the proposed project could provide a useful tool to safeguard equal opportunities to ensure health for all and to ensure equal care in the Netherlands.

Planned activities
- A systematic literature review directed at the cross- relationship between the physical. social and cognitive skills of elderly outpatients, the pharmaceutical aspects of oral medicines and medication self-
- management.
- Patient study on the suitability of the way patients are handling their medication in daily practice and are dealing with any problems.
- Patient study on the suitability of Baxter packs as an intervention to allow patients that are otherwise not able to self-mange their medication to refrain from further health care support or relocation in an institution.
- A patient study to identify the characteristics of a push-through blister pack and the medicinal product inside that pack in relation to the ease of ejecting the medicinal product through the ruptarable layer of this blister.
- Qualitative questionnaire study relating to the health literacy.
- Development for a decision tree for the 'elderly proofness' of medicines.

Planned products
- Tool to assess the elderly proofness of medicines.
- PhD thesis.
- At least three international peer reviewed publications.

Foreseen follow-up
The results from this project can be translated into interventions that consolidate into the equal quality of pharmaceutical care for elderly. The European Medicines Agency (EMA) establishes scientific guidelines to ensure the

development of safe and efficacious medicines with an appropriate product design. The results of this project will contribute to the discussion whether it is necessary to develop a quality guideline on the pharmaceutical development of medicines for use by the elderly and will provide the expert knowledge for RIVM members of staff to act as a reporter for such a guideline.

The results of this project may also lead to adjustment of the current benefit-risk assessment of medicines to include a specific discussion on the 'elderly proofness' of medicines. The results of this study will be used to advice the Inspectorate and Ministry of Health, Welfare and Sport in pharma policy decisions relating to medicines for use by the elderly or any other means that favours the adequate and correct use of these medicines.

Further, this project will allow the RIVM to keep up to date with health literacy research and to gain an expert position in this field. Health literacy is considered a prerequisite for a well functioning health care system that relies on the individual responsibility for health.

5 Healthy and sustainable living environments (HSL)

5.1 Strategic aims

Societal impact
In recent years, the concept of 'sustainability' has gained prominence and reached the top of political agendas. Most people now recognize that continuing our current economical life style would harm valuable ecosystems and jeopardize the prosperity and well-being of future generations. Sustainability means that negative effects of human behaviour will not be transferred to the future or to another location. In the case of transfer towards the future, long term effects on multiple generations are concerned. There is no simple way to determine when human behaviour is 'sustainable'.

While climate change currently attracts most of the attention, it is also apparent that we are using up many of the world's natural resources and that some environmental changes will prove to be irreversible. The doom scenarios of the consequences of our current behaviour now have worldwide attention. Concrete effects of human-induced environmental change seem no longer restricted to the distant future: droughts, floods and migrating infectious disease vector species have already been attributed to environmental change. Especially in the Netherlands, a country with a high population density, there is a rising concern and a need for research to obtain more information about healthy (urban) living environments of future generations. The time is right for taking concrete steps toward a more sustainable world.

Description and impact in relation to RIVM tasks
Over time, the term 'sustainability' has come to embrace various concepts. Many of those are relevant to RIVM's core business. Sustainable ecosystems are of current research concern, with particular emphasis on 'ecosystem services'. Examples are sustainable food production, production of drinking water and clean air. Emphasis is also placed on sustainability of food and long term health effects of products in particular. Moreover, studies of sustainable performance in are of recent concern: for example, chemicals such as antibiotics and medicinal products do not belong in the natural environment, but in reality release negative effects on the ecosystem and their own curative effectiveness. This leaves another research factor worthy of investment: to increase knowledge about sustainable and healthy local living environments, which are under considerable pressure of the densely populated Netherlands.

Focus and future direction of projects
In this research theme, various RIVM Divisions could develop new approaches to the assessment of sustainability trends and measures. Cost/benefit analyses could be significant elements of such sustainability assessment approaches. Further defining and measuring 'environmental capacity' could be a subject for study under this research theme. Such expertise – including newly developed measuring criteria – could eventually provide guidance for action and incorporation into integrated risk-benefit assessments.

Sustainability is a global concept, and choices in one country will affect other countries. Therefore, (inter)national *collaboration* is a *must* within this research theme. The research theme will focus mostly on the living environment (*planet*) and the relation to human health (*people*) as topics of research and not so much on areas such as robust, sustainable systems in general (for example the social and economical perspective, *profit*).

International connections
Sustainability is high on international agendas. For example, in its medium-term plans, the European Commission's Directorate-General Environment lists 'sustainable use of natural resources' as priority number 4. Within its strategies, the European Environment Agency (EEA) mentions 'sustainable consumption and production' as a key priority next to 'climate change, ecosystems and air quality'. Such priority definitions will help create funding opportunities for research proposals, e.g. through the EU's 7th Framework Programme (FP7) or LIFE, the EU's financial instrument supporting environmental and nature conservation projects. FP7's 2010 Work Programme contains calls for proposals in the areas of 'forecasting and assessment tools for sustainable development' and 'modelling change and sustainable behaviour'.

Keywords
(ecological) transfer, capacity, long-term effects, cost/benefit ratio, assessment tools, win-win situation, consumers, (animal) welfare, (local) living environment, use of space, natural resources, energy, nutrition, ecosystems, noise, earth observation, environmental hygiene, climate change, CO_2-balancing

5.2 List HSL

Number	Title	Project leader	Int.
S/260246	Context of health disparities	Annemarie Ruijsbroek	
S/330126	Human entero- (EV)and parechoviruses (HPeV) in water	Saskia Rutjes	
S/607020	Measurably sustainable	Leo Posthuma	
S/607021	Climate cascades (Impact of toxic substances and pathogens on man and ecosystems)	Ton de Nijs	
S/607022	Quantification of ecosystem services for environmental assessment and planning (QESAP)	Michiel Rutgers	
S/680021	Light pollution and the absence of darkness - LightPAD	Dorien Lolkema	
S/680022	Toward a sustainable acoustical environment (TASTE)	Jan Jabben	

Int. = international project cofinanced by SOR-budget

5.3 Summaries

Title:	**Context of health disparities**
Project number:	**S/260246**
Project leader:	Drs. J.M.H. Ruijsbroek (Annemarie) (V&Z-PZO)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 649,100

Motivation

A sustainable society is a healthy society, with no trade-off at specific subpopulations. To promote sustainable public health for the whole population, avoidable health differences should be tackled. In the Netherlands, like in other countries, health disparities are large and persistent: the gap in life expectancy between the highest and lowest educated groups has recently been calculated to be as much as seven years for men and six years for women. Recently, socioeconomic health disparities have returned to the Dutch political agenda, and also the European Union (EU) developed a strategy to reduce health disparities.

The focus of the World Health Organisation (WHO) commission on Social Determinants of Health on the wide range of social determinants of health brings the role of the social and physical environment to the agenda. These social and physical circumstances are deemed mostly responsible for health disparities between socioeconomic groups. However, less attention has been paid to identify the pathways through which the social and the physical environment influence the development and persistence of health disparities.

The social environment covers the social groups we belong to, the neighbourhoods we live in, our work environment etc. This social context influences our lifestyle and health. A healthy lifestyle is not just an individual choice, but takes place in a social context, which includes social norms, support, information, social control, etc. The concept of social capital comprises these dimensions of the social environment. Social capital refers to the benefits one can experience from contacts with other people. In this project we use the concept of social capital to conceptualize the social environment. We focus on individual social capital.

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The physical environment has both a direct impact on health through exposure to chemical, physical and biological factors and indirect impact through stress of e.g. noise, and stress reduction through access to quiet, green space and water or through lifestyle. Health inequalities may partly be explained by socioeconomic differences in the physical living environment. In the Netherlands, there are indications that the environmental burdens and benefits are unequally distributed among socioeconomic groups. As yet, the domain of environmental equity, seems to be fairly separate from health inequality research. A more integrated approach, where insights into differences in the quality of the living environment between socioeconomic groups are extended to effects on health, can help to explain health disparities, and is therefore part of this project.

Aim of the project

The aim of this study is to investigate the role of the social and physical environment in the development and persistence of socioeconomic health

differences in the Netherlands and to find leads for policy and interventions in reducing health disparities.
Specific objectives are:

- To develop a multidisciplinary conceptual framework with particular focus on the mechanisms by which social and physical environment characteristics influence socioeconomic health differences.
- To find out what constitutes the social environment of different socioeconomic groups, according to their own perception. These new views will be incorporated in an elaborated version of the conceptual framework.
- To explore the role of geographic locations, such as the neighbourhood, for the quality of the social and physical environment of different socioeconomic groups, and at which geographical scale the mechanisms operate.
- To gain insight in the way the physical environment influences the magnitude and quality of the social environment and its effect on people's lifestyle and health.

Strategic and innovative aspects

This project will add to the current scientific knowledge by developing and empirically testing a conceptual framework that combines sociological constructs and insights from environmental equity studies with public health models with the specific goal to differentiate between socioeconomic groups. This project is the next step in the translation of the rather recently developed concept of social determinants of health into practice, in particular the interaction between the social and physical environment in relation to health disparities. Since health disparities are back on the agenda of the policymakers both locally and internationally, it is important for the RIVM to keep up to date and to maintain our scientific standing.

Planned activities

- We will empirically test the conceptual model on social capital and health behaviour, which we have developed in the past years. With this model we will test which elements of social capital are related to people's lifestyle and whether this differentiates between socioeconomic groups.
- We will explore to what extent social networks of different socioeconomic groups are locally embedded, and whether this relates to the quality of the social networks. The conceptual model will be extended with concepts and theories from environmental equity literature.
- Focus group interviews and in-depth interviews are carried out to complement theory from activities mentioned above, with reality and to find out what constitutes the social environment according to socioeconomic groups themselves. We will examine whether social networks of different socioeconomic groups are located within neighbourhoods or on a wider geographical scale, and the impact of the physical environment on the individual social capital. Also work-related social networks will be identified.
- After this we will extend the model with the findings from the qualitative data analyses. This final conceptual framework will be translated into questionnaires and additional data will be collected by using the cohort study Healthy Life in an Urban Setting (HELIUS) of the University of Amsterdam.
- Finally the interaction between the different dimensions of the social environment with the local physical environment in affecting the lifestyle and health of different SES groups (Social Economic Status) is explored empirically. We will explore whether the environmental aspects of neighbourhoods interact with the social environment of people and whether this adds extra health risks for disadvantaged groups.

Planned products

- An empirically tested conceptual framework on social determinants of health for different socioeconomic groups.
- A series of peer reviewed publications in international journals, resulting in a PhD thesis. It is anticipated that each research phase results in at least one manuscript.
- A (inter)national and interdisciplinary network of experts on social determinants of health inequalities and environmental inequalities.
- Strong collaborations (University of Amsterdam, University of Utrecht, Harvard).

Foreseen follow-up

Our findings will provide insights on how the physical and social environment may cause health disparities, resulting in leads for policymakers how to tackle health disparities. With the findings from this project we wish to inspire the intersectoral approach that is deemed indispensable to address existing health differences, leading to new assignments from multiple ministries, such as the Ministry of Health, Welfare and Sport, the Ministry of Social Affairs and Employment and the Ministry of Infrastructure and the Environment, and potentially from the WHO and EU.
Furthermore, research on the relations between the social and physical environment and health and health disparities is internationally innovative, given the general lack of knowledge on this topic.

Title:	**Human entero- (EV)and parechoviruses (HPeV) in water**
Project number:	**S/330126**
Project leader:	Dr. S.A. Rutjes (Saskia) (CIb-LZO)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 434,000

Motivation

In the Netherlands, the reported number of enterovirus and parechovirus cases has increased over the past years to 1224 and 373, respectively, in 2009. This can be explained from increased recognition of the infection by clinicians and a grown request for testing of patient samples and improved diagnostic methods. Nevertheless, the absolute numbers of enterovirus and parechovirus disease cases point to a serious public health concern in the Netherlands. Detectable enteroviruses can now be identified in patients with mild to severe disease in which previously no causative agent could be identified. In addition, with the recent developments in molecular tools, many new viruses have been identified globally of which several are associated with severe symptoms. In particular, the new human enteroviruses (e.g. enterovirus 71) and parechoviruses are emerging and cause very severe disease, such as meningitis, and even death, in particular in very young children.
The mode of enterovirus and parechovirus transmission is thought to be through person-to-person contact. More specifically, transmission may be via the fecal-oral route which suggests that exposure to viruses via water is a realistic threat. Nevertheless, to which extent the presence of these viruses in water contributes to the number of infections and disease in humans in the Netherlands is yet unclear.

Enteric viruses, including enteroviruses and parechoviruses, are excreted to high concentrations in the faeces. High concentrations of viruses may enter the sewage treatment and still high concentrations of viruses remain in the treated sewage. Those viruses, in (un)treated sewage, are discharged onto surface water and are further distributed by means of surface water flows. Surface water is used as source water for the production of drinking water, used for recreational purposes, for irrigation of crops and for shellfish cultivation for human consumption. More specifically, enteroviruses have been detected in untreated and treated sewage and in surface waters.
In our laboratory, multiple cell culture assays are applied to obtain data on infectivity and quantitative data of enteroviruses in environmental sources. However, no data exist on virus types. Such data can be used for quantitative microbial risk assessment (QMRA) studies, which may unravel the transmission of human enteroviruses and parechoviruses through water. Retrospective studies on known and possibly newly identified enteroviruses and parechoviruses in archival water concentrates, may provide information about geographic and seasonal distribution of emerging or previously undetectable viral strains.

Aim of the project
The aim of this study is determine, whether the presence of enteroviruses and parechoviruses in the aquatic environment poses a problem to public health. The multidisciplinary approach to clarify the possible association of enteroviruses and parechoviruses in water and patients addresses the following specific objectives:

- Virus discovery: explore the diversity of enteroviruses and parechoviruses in aquatic environments (e.g. metagenomics) which may lead to the discovery of new picornaviruses.
- Environmental surveillance: to estimate from the numbers of enteroviruses in wastewater and faeces of vaccinated individuals the value of environmental surveillance.
- Retrospective study: determine if, when and under what circumstances novel enteroviruses and parechoviruses, first occurred in archival water samples to determine their potential for emergence.
- Molecular tracing: determine if human isolates can be molecularly traced to associated water samples.
- Epidemiological study: determine if drinking water exceedances coincide with increased enterovirus disease symptoms.
- QMRA: Quantify infectious enteroviruses and parechoviruses in different water samples using newly available cell-culture methods. Subsequently estimating the infection risk from enteroviruses in water to which humans are exposed.
- Preventive measures: evaluate effectiveness of advanced water treatment processes, or other interventions, with respect to known and newly discovered enterovirus load reduction.

Strategic and innovative aspects
This research is on the challenging interface between environment and public health, new insights in transmission routes will enable development of new intervention methods and possibly reduce disease burden. We will use this project to strengthen bonds and exploit the benefits of close cooperation between environmental enterovirologists, surveillance and molecular enterovirologist and clinical enterovirologists to obtain in depth knowledge on the relevance of environmental prevalence and possible transmission routes of these viruses. Innovative aspects are the metagenomics approach for the establishment of the phylogenetic link between human and environmental enterovirus isolates and the sequencing and typing of archived samples to help

in determining evolutionary rate and common ancestors of pathogenic enteroviruses.

Planned activities
The seven proposed research tasks will serve as a guideline for the planning during this project. Planned activities are:
- Detection of enteroviruses and parechoviruses in different water samples followed by molecular typing for identification.
- Estimation of the sensitivity of environmental surveillance in comparison to other modes of surveillance.
- Molecular typing methods will be applied on archival water samples to identify the enteroviruses and parechoviruses present in these samples.
- Comparing sequences obtained from human isolates to those obtained from water samples.
- Correlation of geographical drinking water quality data with clinical data.
- Estimating infection risks from enteroviruses in water to which humans are exposed.
- Evaluation of improved treatment processes for enterovirus reduction.

Planned products
- Optimized methods for quantitative microbial risk assessment (QMRA).
- Standard operating procedures (SOPs) for detection and identification of enteroviruses and human parechoviruses.
- Four publications in peer reviewed journals.
- PhD thesis.
- Presentations at international scientific meetings and conferences such as the IWA-HRWM (International water association – health related water microbiology) and EUROPIC (Conference of the European study group on the molecular biology of picornaviruses).

Foreseen follow-up
The results obtained in this project will possibly lead to new initiatives and new (inter)national contacts for cooperation and the possible start of new research projects. Furthermore, the Ministry of Infrastructure and the Environment (IenM) can make decisions on interventions for enteroviruses in water (for the need of further and specific research projects).

Title:	**Measurably sustainable**
Project number:	**S/607020**
Project leader:	Dr. L. Posthuma (Leo) (MEV-LER)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 900,000

Motivation
Sustainability has been made corner stone of Dutch environment policy. In this context sustainability (i.e. - of developments, actions, systems, choices, products) has been operationally defined for the purpose of environmental policymaking by the Ministry of Infrastructure and the Environment (IenM) as the extent to which our activities here (place) and now (time) affect others, living elsewhere or in future times: choices made by us should not shift burdens to our neighbours or our children. IenM's implementation of sustainability into practical policymaking consciously focuses on the 'planet' aspect and on parts of the 'people' aspect of sustainability, at the expense of

the 'profit' aspect. Although this greatly helps in making practical choices, sustainability remains a hard-to-quantify subject and results of sustainability based policy cannot be measured directly.
Adopting IenM's operational definition of sustainability of action, metrics for measuring and comparing sustainability options are needed: metrics that would enable our (inter)national clients to make quantitative comparisons in practical environmental decision-making. The project builds on the theoretical concepts of sustainability developed in the recent past, combining these with methods that have proven their utility in Life Cycle Analysis of goods and services.

Aim of the project
Primary objective of this project is to produce and deliver a scientifically sound calculation and visualization tool, which can be used by environmental professionals and the general public in support of making practical choices in sustainable action and sustainable development. The tool will give decision-makers the possibility to decide which, of the options to choose from is quantitatively more sustainable. The tool is to be used in answering practical questions; questions of the 'which-option-is-more-sustainable?' The tool is to be used by all those who, in their individual or professional life, wish to act sustainable. While it is recognized that this applies to any individual – therefore, the general public is identified as major users of the tool – the project focuses on professional users in regulatory offices and consultancy organizations.
Committed entirely to scientific soundness, the primary ambition of the project is to serve environmental professionals with a practical decision support instrument.

Strategic and innovative aspects
Concepts and models for sustainability assessments have been developed and applied in policy analyses and isolated aspects of sustainability have been quantified successfully. No integrated, practice-oriented approach to quantifying and aggregating the entire spectrum of relevant sustainability end points has been reported so far. The proposed calculation tool integrates various and different difficult-to-compare aspects of sustainability into one final (semi-) quantitative assessment, offering quantitative support to environmental decision-making, aimed at enhancing sustainability. In addition, it provides the link between activity and environmental pressures as a necessary step in coming up with sustainability scores. Unlike approaches to quantitative assessment taken earlier, which have often been aimed at solving big policy issues and applications of which have (consequently) been limited to specific purposes, the sustainability calculation tool aims to provide a general framework for making quantitative comparisons of sustainability aspects in environmental policy decisions, allowing end users to address practical questions. Unlike currently available concepts and methodologies, the proposed assessment system includes time aspects involved and deals with the spatial scales covered, allowing (semi)quantitative comparison of burden shifts to neighbours or children.

Planned activities
- Inventory of the sustainability issues for which the intended end users of the calculation tool need quantifications.
- Analysis of the sustainability endpoints to be addressed. We will define/select a minimum set of mutually independent indicators and develop suitable metrics for these end points.

- Metrics for each of the defined endpoints are worked out, taking methods currently used in Life Cycle Impact Assessment as starting point.
- Possibilities for modelling the identified sustainability endpoints in a coherent calculation and visualization tool are explored and developed.

Finally, he integrated (semi-) quantitative assessment framework is coded into a computer tool and documented for use by end users.

Planned products

Main product of this project is the calculation tool for quantifying sustainable action/development. All other specific deliverables named below contribute to this main.

- Sustainability Calculation Tool. Web-based calculation tool for quantification of options for sustainable actions/developments, to be used by environmental professionals and the general public.
- Documentation and User Manual. Document that introduces, describes, guides and technically explains the Sustainability Calculation Tool.
- Short list of sustainability indicators. Minimum set of (independent) indicators of sustainability, for which metrics are to be operationalized.
- Operational models for calculating sustainability.
- A PhD thesis.
- Approximately ten scientific journal papers.

Foreseen follow-up

The project is to deliver a scientifically well-thought integrated system for measuring sustainability of action/development, for versatile practical use in various ministerial policy dossiers. It is envisaged that the tool will be implemented as an internet-accessible application, to be used by environmental professionals, as well as by members of the general public for expressing the extent to which our activities here and now affect others there and then.

Integrating the most relevant aspects of sustainability, the method will find application as a basis for practical environmental decision-making. For example, the calculation tool will be applied to improve sustainability in governmental purchasing policy. With the tool developed, RIVM will be ready to serve IenM and other ministries with decision support in the form of quantitative sustainability comparison of environmental policy options. Interest in this project has been expressed by the new Department of sustainability assessment at the Joint Research Centre of the European commission (JRC) in Ispra, Italy. Based on this work, future cooperation in exploring possibilities for use of LCA-based calculation tools in promoting sustainable consumption are foreseen.

Title:	**Climate cascades (Impact of toxic substances and pathogens on man and ecosystems)**
Project number:	**S/607021**
Project leader:	Dr. A.C.M. de Nijs (Ton) (MEV-LER)
Start:	01-01-2011
End:	31-12-2015
Total SOR-budget:	€ 994,916

Motivation

According to the Dutch Meteorological Institute, future summers in the Netherlands will resemble those currently occurring in the Po Valley and future winters will be similar to those in the Paris region. Average temperatures are

predicted to rise, summers may become dryer, whereas winters may become wetter. The number of heavy rainfall events occurring throughout the entire year is expected to increase, whereby flooding will occur more often.
These changing meteorological conditions in the Netherlands will affect the soil, groundwater and surface water, impacting on terrestrial and aquatic ecosystems as well as public health.
Soil formation, in particular the production and degradation of organic matter, strongly depends on climate, namely, on temperature, precipitation rates and soil moisture. These three aspects of climate affect vegetation cover, food-web structure and biological, chemical and physical process rates. Soil organic matter content is likely to change in the future. The decay of soil organic matter may release associated chemicals and metals, such as copper and cadmium. Changing soil structure may also promote the transport of toxic substances and waterborne pathogenic microorganisms. Moreover, pathogen levels will change due to higher temperatures.

Although changes in climate may be gradual, it is more likely that they will be abrupt. If our soils change, the composition of our groundwater and surface water will change. Depending on the timeframe of the expected climatic changes, the organic carbon content, pH and alkalinity of surface water bodies will increase or decrease, thereby directly affecting the toxicity of many metals in the surface water.

Aim of the project
The overall objective of this study is: to assess the potential impacts of toxic substances and waterborne pathogens on man and terrestrial and aquatic ecosystems that result from the effects of climate change on soil, groundwater and surface water at the river basin scale.

Key questions to be addressed are:
- What are the effects of climate change (including the potential non-linear effects of abrupt climatic changes) in terms of soil management and mitigation measures on the biogeochemical cycles of carbon, nitrogen, phosphorous and on the composition of the soil, groundwater and surface water?
- How will the predicted changes in the composition of soil, groundwater and surface water affect the distribution of toxicants and pathogens in the environment following gradual as well as abrupt climatic changes?
- How can future changes in the environmental distribution of toxicants and/or pathogens affect man and ecosystems?

Using these key questions as a basis, our aim is to develop a modelling framework consisting of a dynamic, spatially detailed river basin model and a probabilistic risk assessment model. The river basin model will be used to estimate future distributions of soil, groundwater and water parameters needed in the risk assessment model.

Strategic and innovative aspects
The results of this project will be of strategic relevance to the current tasks and responsibilities of the RIVM and of major importance to assessments of the risks of exposure to toxicants and pathogens to man and ecosystems. In addition, the data obtained in this study will make a positive contribution to the performance of future tasks, such as the evaluation of climate change mitigation and adaptation strategies relevant to public health and the health of ecosystems. This study is the first to attempt an integrated multidisciplinary analysis and assessment of the influence of climate change on soil, groundwater and surface water composition, including the redistribution of toxic substances and pathogens and their ultimate impacts on man and ecosystems.

Planned activities

- Development of modelling framework: the framework should describe the relevant parameters at the interface between the two models.
- Future developments: future developments concerning changes in climate (rainfall and temperature), land use and management, water and soil policies and mitigation and adaptation measures will be retrieved from the literature.
- Development of the river basin model: an integrated dynamic and spatially detailed River Basin Model will be developed to estimate future developments in soil, groundwater and surface water composition due to climate, land-use and management change, water and soil policies and mitigation and adaptation measures.
- Development of the risk assessment model: the risk assessment model will be a probabilistic model, enabling the assessment of the risk of future developments in climate, land use and management and water and soil policies relevant to both humans and terrestrial and aquatic ecosystems.
- Integration and Assessment: the river basin model and risk assessment model will be integrated. The plausibility of the results of the integrated system will be checked. At this stage, a limited number of relevant scenarios will be simulated by assessing the impacts and risks of climate change on man and ecosystems.

Planned products

- A modelling framework.
- Database on future developments and their translation into the model parameters, logical scenarios and input for the river basin and risk assessment model.
- A river basin model.
- Risk assessment model describing the risk to human health and ecosystems from exposure to toxic substances and pathogens due to climate change and two peer reviewed publications.
- Integration of the river basin and risk assessment model, the simulation of relevant scenarios and the risk of toxic substances and pathogens to man and ecosystems.
- At least eight peer reviewed publications.
- Two theses.

Foreseen follow-up

The European Water Frame Directive, the Ground Water Directive as well as the Drinking Water Act define the required status of surface water, groundwater and drinking water. Climate change may have large effects on all water resources and may result in additional measures. With the results from this study, we will be able to evaluate the potential impacts of various measures addressing soil, groundwater and surface water quality, toxic substance and pathogens in relation to climate change. With the instruments developed in the project we will be able to provide national and European authorities with assessments of the potential risks of climate change on man and terrestrial and aquatic ecosystems.

Title:	**Quantification of ecosystem services for environmental assessment and planning (QESAP)**
Project number:	**S/607022**
Project leader:	Dr. M. Rutgers (Michiel) (MEV-LER)
Start:	01-01-2011
End:	31-12-2015
Total SOR-budget:	€ 959,000

Motivation

The continuing growth of human population, and, to a lesser extent, that of its average prosperity will further increase the dependency of society on the environment quality, whereas the same environment is facing increasing impacts from management practices. With sustainable management of the environment and its functioning, mankind can optimally profit from its capacity to provide Ecosystem Services (ES), for instance to support health, provide clean water, maintain clean groundwater and support production of food and fibre. A new focus on ES will provide the insight on where and how management can be made sustainable. Until recently, there was little need for quantification and accounting, since the global provisioning of ES seemed to be almost unbreakable (with exceptions, like erosion and pollution effects on food production, and climate change effects on the water cycle). In addition, farmers and fishermen seem to be aware of the ecosystem margins to produce biomass, but they unfortunately adopted a strategy, which actually led to increasing dependency on excessive land and fisheries management, rather than to profit optimally from ES in a sustainable way.

Consequently, there is an urgent need to develop new scientific concepts for quantification, assessing, managing and planning of ES, for a sustainable use and design of our environment, now and in the future. As such this will contribute to a paradigm shift for environmental assessment and valuation of our natural capital, concordant with the shift in environmental policy and management. Quantification of ES will provide a transparent and a rational underpinning of alternatives in environmental decisions, and can thus be used to define sustainability goals, for a broad range of stakeholders and end-users on different spatial and temporal scales. For this reason, integrated ES quantification schemes should be regarded as a tool for sustainability development at the interface of society and science - science alone will not provide motivation to incorporate sustainability measures in our daily live.

Aim of the project

The objective of this project is to develop general concepts for quantification of ES, and to test and validate these concepts using soil data and models. We focus on soils because the soil is the basis of all terrestrial ecosystems and RIVM has unique access to soil data, modelling expertise and measurement schemes. Also elements for spatial and temporal facets of sustainable use and management of ES will be produced.

The project is divided into three parallel main streams, each with objectives:

- Indicators and measurement of ES (Tools). The objective is to develop practical tools for quantification of ES by using existing data from a suite of indicators, data from monitoring networks and by combining the results with new integrated tools for quantification of ES.
- Development of theory in relation to ES (Modelling and Theory). The objective is to validate the ES concept via linking ecosystem models to functioning, including the link between ecosystem structure and ecosystem functioning.

- Assessment, management and planning issues (Planning). The objective is to design assessment and classification schemes, recovery modules and to combine them to spatially explicit tools for planning and managing of ES. ES will be valued also through cost benefit analysis.

Strategic and innovative aspects
Ecosystem services fill the gap between ecology, environmental policy and management. This gap materialized recently as reflection of the transition from an environmental stress oriented policy towards sustainable use of ES. Apparently, there is still a lack of understanding how to bridge this gap. This project is optimally equipped for producing building blocks, due to the strong position in science and policy oriented public platforms of the RIVM. Moreover the RIVM is currently producing a large database with environmental ES–oriented metadata from several monitoring activities.

Planned activities
- An inventory of options for collaboration, and a kick off meeting for setting the priorities in the project is planned.
- From soil data to ecosystem services; tools to quantify current and future conditions of the environment. In this part of the project the principles, opportunities and limitations to quantify ES will be explored. There is a need for new indicators, since current indicators and monitoring activities are mainly focusing on exposure and impact.
- Modelling and understanding of the functioning of ecosystems. Our knowledge of the relationships between the performance of ES and the state of the ecosystem including its functioning is limited. In this part of the project the focus will be on the underpinning of the concept via appropriate theories and models of ecosystem functioning.
- Elements for assessment and planning ecosystem services and sustainability. Only with suitable and transparent quantification, classification, assessment and mapping schemes. Existing ecosystem prediction and classification systems will be modified to fit also ES. Cost benefit analysis will be considered as a tool for providing an economic dimension of ES.

Planned products
- Scientific sound concepts and practical tools related to the quantification, validation, classification, assessment and planning of ES.
- PhD thesis containing four manuscripts and five scientific publications in a range of journals.
- A comprehensive analysis of state-of-the-art, collaboration options.
- Results on ES will also be translated and communicated to the public and people participating in ES management through non-scientific publications and workshops.

Foreseen follow-up
The RIVM will benefit from the project through gaining a strong position in a new research area, connected to sustainability and system research. In the near future this will become fundamental for underpinning modern environmental policy and management. Consequently, more dedicated projects will appear and RIVM and co-workers will show up as preferred knowledge partners at a national level.
The collaborating partners also will benefit from QESAP (Quantification of ecosystem services for environmental assessment and planning), because of the access to environmental data and RIVM's scientific and policy-oriented expertise in this area.

Title:	**Light pollution and the absence of darkness (LightPAD)**
Project number:	**S/680021**
Project leader:	Drs. D.E. Lolkema (Dorien) (MEV-CMM)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 810,558

Motivation

The world at night is bright today. Pictures from space show us beautifully and strikingly the modern human footprint by how we illuminate our night. One of the brightest spots on these maps comes from the Netherlands, a very densely populated area. Although the need for artificial light in populated areas is beyond question, there are also adverse effects of night time light on flora and fauna as well as on humans. Because industrial areas, nature reserve areas, residence areas and greenhouses lie close together in the Netherlands, both positive and negative aspects of artificial light at night are strongly intermingled here.

Currently, actual levels and the variability of local night sky brightness in the Netherlands are not well known. Furthermore, the actual impact of artificial night time lighting on ecosystems and human health in the Netherlands is also far from known. Finally, the impact of meteorological influences on the diffusion of light from artificial light sources and hence the levels of night sky brightness at large distances from these sources is not understood. The latter is necessary to make accurate predictions of night sky brightness based on knowledge of the distribution of light sources. However, in the meantime, policy is being made on the impact of artificial light, both on national and local level. Questions therefore that will arise in the near future include: What is the level and variability of local night sky brightness in the Netherlands? What is the impact on ecosystems and human health in the Netherlands? This project aims to be ready for these questions.

Aim of the project

This project aims at an integrated approach of night sky lighting and its consequences, tailored to the Dutch situation, in support of recent policy developments. Specific objectives:

- Investigation of the actual levels and variability of local night sky brightness in the Netherlands.
- Investigation of the relations between meteorological and atmospheric parameters and night sky brightness.
- Investigation of the influence of large sources of night time light (city, industrial area, highway) on their surroundings.
- Night sky brightness map for the Netherlands.
- Assessing the impact of artificial night time lighting on ecosystems and human health in the Netherlands.

Strategic and innovative aspects

Research on light pollution and its consequences has just started. Meanwhile, political interest is increasing. With this project, we will focus on questions regarding the negative aspects of artificial night time lighting that will arise in the near future for instance:

- What is the level and variability of local night sky brightness in the Netherlands?
- What is the impact on ecosystems and human health in the Netherlands?

With this project, RIVM will broaden the scope of the current research on light pollution and strengthen its international scientific position on the investigation of light pollution and its consequences.

Planned activities

- Night sky brightness measurements will be performed at six locations in the Netherlands during the first three years of the project. These locations will be co-located with the locations of the Wageningen University (WUR) research, where possible.
- Analysis and interpretation of the measurements. A comparison with earth observation of night time light emission will be made.
- Continuation of the night sky brightness measurements started in 2010, at the advanced remote sensing site Cabauw.
- Analysis and interpretation of the measurements, combined with the other measurements performed at this location, in order to formulate the relations between meteorological and atmospheric parameters and night sky brightness. Interaction with development of a night sky brightness model.
- Night sky brightness and extinction measurements will be performed at several distances from three typical large sources of night time lighting (city, industrial area, highway) during different atmospheric conditions. Interaction with development of a night sky brightness model.
- A literature review for ecological consequences of artificial night time lighting will be performed and the results will be judged for their relevance to the Dutch situation.
- A literature review to obtain an overview of the health consequences of artificial night time lighting.
- An internet questionnaire will be carried out among a sample of the Dutch population assessing the perceptual aspects of artificial night time lighting.
- The results of the literature reviews and the internet questionnaire will be used together with the night sky brightness model and the earth observation of artificial night time lighting to estimate the impact of artificial night time light on nature reserve areas in the Netherlands and to try to formulate an exposure effect relation between artificial night time light and annoyance.
- Midterm, a workshop will be organized for relevant parties in- and outside this project. Depending on the results of this workshop, the project planning for the second half might be changed.
- At the end of the project, a final presentation will be given to all relevant parties.

Planned products

- Seven scientific publications and a report.
- A night sky brightness map for the Netherlands.
- Two databases.
- A night sky brightness model.

Foreseen follow-up

Results from this project, ranging from night sky brightness measurements to consequences of artificial night time light on ecosystems and human health, will be used together with a night sky brightness model and with earth observation of artificial night time lighting to estimate the impact of artificial night time light on nature reserve areas in the Netherlands and will be used to to try to formulate an exposure effect relation between artificial night time light and annoyance.

Possible new assignments include:
- Installation of a night sky brightness monitoring network.
- Improving the night sky brightness model.
- Monitoring the impact of artificial night time lighting on ecosystems and human health.
- Validation of earth observation of artificial night time lighting.

Title:	**Toward a sustainable acoustical environment (TASTE)**
Project number:	**S/680022**
Project leader:	Ir. J. Jabben (Jan) (MEV-CMM)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 854,600

Motivation

Due to ongoing urbanization, environmental noise has become a major burden for the liveability and general well-being of the residential population. Unless more effective noise policies are implemented, environmental noise emissions will increase and, moreover, areas where people can enjoy quiet will change and will become scarce. This is problematic, since there are serious scientific findings that spending time in areas with relatively low levels of noise is beneficial for human health and well-being.

While reducing noise levels has been the focus of Dutch noise policy, it is well known that reducing noise levels (expressed in L_{den}) is not always feasible and cost-effective. Besides that, it can be doubted if the standard L_{den} indicator, that rates the yearly average of time varying noise levels at the façades of dwellings, is a good predictor for perceived urban acoustical quality. What is needed is a broadened understanding of the meaning of urban acoustical quality in general that includes temporal aspects of noise levels and the meaning of areas with high acoustical quality.

A major obstacle with regard to the effects of spending time in areas with relatively low noise levels is the identification of such areas. An assessment based exclusively on noise levels provides only a limited reflection.

Supplementing conventional noise research with ideas and techniques from the sounds cape field could be valuable: as opposed to conventional noise research, the focus in this project is on sounds of preference (wanted sounds). In view of the observations outlined above, there is a need to extend conventional noise management with a generalized view on urban acoustical quality.

Aim of the project

The aim of this project is to obtain a generalized conceptual understanding of high acoustical quality of urban areas and provide new insights and tools that can contribute to a sustainable acoustical environment.

Specific objectives are:
- To develop generalized noise indicators that can be used to obtain a more complete characterization of the acoustical quality of a specified urban area.
- To assess the optimal scale and composition of specified areas with regard to the correlation of the generalized physical indicators meant above and human perception.
- To fill the knowledge gaps and to explore the effect of access to urban areas with high acoustical quality on people’s perceptions.

Strategic and innovative aspects

By involving Rotterdam environmental protection agency (DCMR) and Municipal Health offices as strategic project partners, the applicability of the new insights in local policies is secured.

At the same time our project strengthens the leading position of RIVM in the field of environmental quality. Moreover, the project also looks into the positive aspects of sound and its potential benefits. In the future this will become more significant: while reducing noise levels has been the focus of the European Noise Directive and Dutch noise policy, it is accepted that reducing noise levels is not always feasible and cost-effective. The innovative nature of the project consists of a generalized integral assessment of environmental noise that will include a broadened view on urban acoustical quality. This will incorporate both a more complete picture of exposure in a variety of aspects and a thorough assessment of the meaning and importance of 'quiet' outdoor areas. New area specific noise indicators will be developed for various exposure characteristics and for areas with relatively low noise levels that may be visited by inhabitants to relax and recover from stress. The multidisciplinary approach where environmental health scientists, town planners, and social geographers collaborate has hardly been carried out in the Netherlands.

Planned activities

The work is divided into three work packages:

WP1 Set up area specific indicators for assessing acoustical quality

- Developing a set of generalized noise indicators that can be used to obtain a more complete characterization of the noise exposure of urban areas.
- Completing and testing the results of a previous feasibility study on the characterization of temporal aspects of noise levels .
- Characterization of the acoustical quality of outdoor urban areas in which the effect of the presence of nearby 'green' areas is being accounted for. developing of objective criteria.

WP2 Perception and experience

- Filling the knowledge gaps and to explore the effect of access to urban areas of high acoustical quality on people's perception and experience of their immediate environment.
- Exploration of the effects of spatial differences between wanted and unwanted sounds on the perception of the immediate sonic environment by statistical analyses, taking into account as much as possible the hierarchical nature of data by using multilevel modelling. Multilevel modelling will enable data gathered at the different aggregation levels (neighbourhoods, postal code areas) and the individual level to be fitted in the same model.

WP3 Relate acoustical sustainability to perception

- Analysis of the relation between people's perception and experience of their immediate living environment and the area specific physical indicators of acoustic quality will be analysed extensively.

Planned products

- A more robust evidence base on the possible link between the effect of access to areas of high acoustical quality and human perception and well-being.
- A typology for urban neighbourhoods will be set up that not only considers the exceeding of L_{den} it values, but also includes extended indicators that allow a more complete characterization of urban acoustical quality.
- Evaluation of effectiveness of current noise policies (standards on dwellings).
- A new vision on effective noise policies.
- Five papers to peer reviewed journals.

Foreseen follow-up

During this project, we expect that the exchange of information and joint research will improve the noise expertise at RIVM and DCMR considerably. For RIVM the data available at DCMR will provide important validation for the tools that were developed for characterizing environmental noise and its meaning for human effects. For DCMR and for local policymakers and town planners in general, new insights into the nature of human complaints and annoyance could help to set up more effective noise action plans. The results of this study will allow policymakers/administrators to exploit broader and more effective tools for improving their environmental noise situation.

The EU's 7th Framework Programme (FP7) now is carried out over 2007-2013. During the project we will look for possibilities of carrying out a follow-up with one or more international partners in the next framework programme. As a follow-up of the in-depth surveys and as a pilot, we suggest to run an activity diary study which aims to investigate the behaviour of people who are supposed to have easy access to urban areas with high acoustical quality and to find out whether this affects their perception of their immediate environment and reduces feelings of stress.

6 Infectious disease dynamics (IDD)

6.1 Strategic aims

Societal impact
Infectious diseases have lost none of their importance to public health, as demonstrated by outbreaks of new agents (such as the new A (H1N1) 'Mexican flu' virus) and the recurrence of 'old' ones like pertussis and sexually transmitted diseases, which still claim numerous victims. Mutating infectious agents continue to find ways around even the most ingenious human strategies to fight them. From time to time, new human disease-causing agents emerge. Environmental changes, including climate change, further affect these dynamic interactions.

Description and impact in relation to RIVM tasks
RIVM's Centre for Infectious Disease Control is mandated to identify, control and prevent outbreaks of infectious diseases. Research in this particular research theme, however, could involve other RIVM divisions such as those studying food safety and the living environment.

Successful infectious disease control requires knowledge about infectious agents, their interaction with human hosts and the environment. There is growing emphasis on zoonoses (human diseases caused by infectious agents originating in other species), because they cause a new threat to public health.

Throughout the last decades, successful methods of infectious disease control have been developed. However, as a response, many infectious agents have developed resistance to antibiotics or antiviral drugs. Vaccines can become less effective as well because of mutations in the infectious agent, as can be seen in viral (influenza) epidemics but in bacterial (pertussis) epidemics as well. Knowing how and how quickly infectious agents move through human populations may help authorities fight and contain outbreaks.

Focus and future direction of projects
The word 'dynamics' is the key concept within this research theme. Changes occur in infectious agents and transmission routes, which increases the urgency to develop new measures for intervention and control. Innovation of knowledge remains of actual concern: epidemiological research, molecular classification as well as modelling research are all increasingly influenced by changes in the environment, globalisation, climate change and target groups.

The 'dynamics' of infectious diseases have a particular effect on zoonoses, vaccination programmes (such as National Vaccination Schemes) and microbial as well as antiviral resistance. Continuous new threats are prone to affect the health of large groups of people. Well-known vaccination schemes are not invulnerable, forcing us to improve the measuring process of protection levels in various regimes (Which are the right markers?). Although our knowledge about the classification of antibiotic resistant bacteria is increasing, the demand for courses of action and control will increase even more in the future. Likewise, antiviral resistance is a considerable matter of future concern.
Alongside these themes the perspective of 'health' could lead to new insights about which mechanisms heighten human resistance against infectious diseases. While the spread of infectious diseases is never restricted by national borders, this research theme holds a substantial international component.

International connections
Infectious diseases may spread widely and rapidly and may even have a global impact. International cooperation is therefore essential, and there are many opportunities to find it. The World Health Organization (WHO), the European

Commission’s Directorate-General for Health and Consumers (DG SANCO) and the European Centre for Disease Prevention and Control (ECDC) all have identified Infectious disease research as a priority.

The WHO sees reduction of the burden of communicable diseases as one of its ‘fundamental needs’. The ECDC, which co-ordinates infectious disease control in the EU, contracts out much of its work.
The EU’s 7th Framework Programme (FP7) offers many opportunities for tenders. For example, FP7’s 2010 Work Programme includes a €18 million call for proposals for research into Pandemic H1N1/09 influenza. The ‘second programme of Community action in the field of health (2008 to 2013)’ offers collaboration opportunities like developing response strategies and mechanisms against communicable diseases.
The European Commission’s Twinning initiative (for EU candidate countries) and the Dutch Ministry of Foreign Affairs’ Matra programme offer opportunities for bilateral collaboration with Central and Eastern European countries to support infectious disease control.

Keywords
change, infectious agent, host, zoonoses, effectiveness, vaccination, vaccines, environment, climate change, resistance, modelling, international, burden of disease, prevention strategy, immunology, food born infections, antibiotics resistance, antibiotics prescription

6.2 List IDD

Number	Title	Project leader	Int.
S/210096	Unveiling the infection dynamics of influenza A	Michiel van Boven	
S/210146	Cytomegalovirus (CMV) infections: disease burden and implications for primary and secondary preventive measures	Hester de Melker	
S/210206	Environmental risk factors for Q fever	Wim van der Hoek	
V/210734/01	EU hepscreen	Susan Hahné	*
S/230176	Assessing population exposure and immunity to new pandemic norovirus strains	Marion Koopmans	
S/230186	Biomarkers for long-term sequels of Q fever	Daan Notermans	
S/230196	Proteomic profiling of XDR TB	Michel Klein	
S/230206	Antivirals against Enteroviruses	Harrie van der Avoort	*
S/230456	Vaccination and pathogen escape (vacscape)	Frits Mooi	
S/330136	Control of tick-borne diseases: shooting the messenger	Hein Sprong	
S/330156	ESBL genes on fresh produce	Hetty Blaak	
V/330524/01/BT	Biotracer, extension 2011	Annemarie Pielaat	*
V/330664/01	SUSCLEAN	Eelco Franz	*

Int. = international project cofinanced by SOR-budget

6.3 Summaries

Title:	**Unveiling the infection dynamics of influenza A**
Project number:	**S/210096**
Project leader:	Dr. R.M. van Boven (Michiel) (CIb-EPI)
Start:	01-01-2011
End:	31-12-2013
Total SOR-budget:	€ 396,700

Motivation
During the 2009 influenza pandemic it became painfully clear that key aspects of influenza A virus epidemiology remained unpredictable. As a consequence, general practitioners, hospitals and especially intensive care units had to prepare for a highly uncertain peak in health care demand that would come within a foreseeable but unknown future. Much concern was focused on the possible devastating consequences of an overwhelmed public health system during the epidemic (notably hospitals). With hindsight, it is clear that these worries did not materialize. It is also clear that quantitative insight in the transmission dynamics of influenza A is urgently needed to improve our ability to predict the onset and size of influenza epidemics.

Aim of the project
In this project we aim to answer a number of important open problems that can be addressed using three unique sets of data that are available at the RIVM. Our specific aim is to identify what drives influenza A transmission dynamics (both seasonal and pandemic), while our larger aim is to develop statistical methods for the analysis of emerging infectious disease data that can handle different types of imperfect information. While our specific aim is already highly ambitious, we believe that our goal can be achieved by step by step analysis of a number of sub-questions:

Specific objectives for seasonal influenza are
- How much of the influenza A transmission dynamics can be attributed to seasonal factors, and how does pre-existing immunity interfere or contribute?
- Which seasonal factors contribute most to the observed epidemic patterns, and can we predict for the Netherlands the environmental conditions and susceptible numbers that allow an epidemic to occur?

Specific objectives for novel influenza A(H1N1) are:
- What is the age-dependent structure of the infection pyramid?
- What were the age-dependent attack rates in the 2009-2010 pandemic, and how do these relate to patterns of infection observed in the 2010-2011 influenza season?
- To what extent can the observed patterns of infection be explained by observed human contact patterns?

Strategic and innovative aspects
This project gauges the infection dynamics of pathogens by combining imperfect data of seemingly incompatible nature (e.g., hospitalization data versus disease data from general practitioners versus serological data from population studies). An assessment of the infection dynamics of pathogens that is based on all available data is essential to reliably evaluate the impact of interventions in the absence of prospective studies with a robust epidemiological design. Currently, there are no methods available to systematically include information from

different sources. Such methods are urgently needed to deal with new, emerging infections.

Planned activities

The analyses make use of data that provide long-term information on yearly influenza epidemics, and detailed information on the novel influenza A(H1N1) epidemic of 2009. In a first step we will use the information from the 2009 novel influenza A(H1N1) pandemic to estimate the age-specific attack rates, transition probabilities of the infection pyramid, and transmission mechanisms. In a second step we will focus on long-term ILI data to try and find patterns in yearly influenza A epidemics.

Recently completed cross-sectional serological studies provide information of the immune status and recent infection history of the Dutch population both before and after the pandemic. Specifically, we have at our disposal information on infection and immune status of the Dutch population in 2006-2007, in July-August 2009, and in April-May 2010. These data will enable the following investigations:

- We will fit an age structured S(E)IR model to the serological data to estimate the attack rates and forces of infection on the different age groups.
- We will use the cross-sectional serological data in conjunction with early case reports and hospitalization data to estimate the shape of the infection pyramid.
- We will use an age structured transmission model to identify which types of contact (physical, conversation, close proximity) are best able to explain the observed patterns of infection.
- In the third year of the project we intend to build a generic framework for estimation of key epidemiological parameters. This will enable rapid advance exploration and testing of novel intervention strategies should the need arise.

Planned products

The results of this project will primarily be laid down in publications in peer reviewed journals. Provisional manuscript titles are given below.

The novel influenza A(H1N1) pandemic:

- Estimation of attack rates and the impact of pre-existing immunity for the novel influenza A(H1N1) pandemic.
- Uncovering the infection pyramid of novel influenza A(H1N1).
- Influenza transmission patterns driven by human contact patterns.

Seasonal influenza:

- Environmental and epidemiological driving variables of influenza A epidemics.
- Estimation of the duration of homo- and heterosubtypic immunity after influenza A infection and vaccination.

Integration of methods and update of influenza A pandemic preparedness models:

- A general statistical framework for inferring infection dynamics from case reports and serological surveys.
- Real-time evaluation of interventions for influenza A epidemics.

Foreseen follow-up

The results of the research outlined proposal will help acquire research funding for new research projects. From a public health perspective we believe that the results of this project will add valuable insights that can be translated in public health policy. We briefly mention three examples:

- With a reliable assessment of the number of susceptibles after the influenza season at hand we will be able to predict whether or not a sizeable influenza epidemic can be expected the next year.

- More precise estimates of the attack rates and infection pressures in different age categories will help to devise more efficient vaccination programmes and to more precisely assess their cost effectiveness.
- A quantitative insight in the role of human contact patterns and in particular the fraction of transmission events that can be explained by the observed contact patterns will help gauge the likely impact of potential control measures aimed at increasing social distances (e.g., school closure).

Title:	**Cytomegalovirus (CMV) infections: disease burden and implications for primary and secondary preventive measures**
Project number:	**S/210146**
Project leader:	Dr. H E. de Melker (Hester) (CIb-EPI)
Start:	01-01-2011
End:	30-04-2015
Total SOR-budget:	€ 848,100

Motivation

Cytomegalovirus (CMV) can be transmitted intrauterine, and is worldwide one of the most common congenital infections. CMV causes a persistent infection and can lead to lifelong (intermittent) shedding. Transmission occurs through shedding of the virus in body fluids during such periods of active replication through close contact with young children or sexual transmission. In a recent retrospective Dutch study using neonatal dried blot spots the preliminary prevalence of congenital infection was estimated at 0.54%. This estimate is in line with an estimated birth prevalence of 0.64%. A follow-up study of Dutch neonates found to have a congenital CMV infection as well as control infants will provide insight into the disease burden including long term sequelae among infants.

A recently developed CMV glycoprotein B vaccine has been tested in a phase 2 trial in seronegative reproductive-aged women and resulted in an estimated 50% vaccine efficacy. This urges the need to explore the potential impact of vaccination on preventing congenital CMV infections.

However, vaccinations with low efficacy could cause the opposite effect as shown in the 1970s with vaccination against rubella. Studies with mathematical transmission models revealed the counterintuitive result that introduction of mass vaccination at a low coverage (or low efficacy) could result in more congenital rubella cases. Increased number of congenital infections in Greece, with mass vaccination at low coverage, proved these theoretical results correct. Therefore introduction of vaccination should be preceded by a careful modelling study that assesses the impact of different vaccination programmes on public health.

This SOR proposal will enable us to judge future prospects of primary and secondary prevention to reduce the health burden of congenital CMV infections.

Aim of the project

Given the limited knowledge in the presumed severe disease burden of CMV in the Netherlands as well as the potential impact of primary prevention by vaccination or secondary prevention by screening we aim to assess:

- The infection frequency of CMV in the population and its determinants (the age-and sex specific seroprevalence of CMV and to study determinants for CMV seroprevalence).
- The disease burden of congenital CMV infection.
- Potential impact of vaccination and neonatal screening (evaluate impact on infection frequency and disease occurrence as result of vaccination, for

various vaccine scenarios and assess the impact of neonatal screening to reduce the proportion of children with long-term sequelae).

Strategic and innovative aspects
By combining the data from seroprevalence study with the contact study, the estimation of the transmission parameters is possible for a low prevalence setting in the Netherlands. Estimated prevalence of congenital CMV in developing countries is likely to be much higher. As clinical and epidemiological patterns of CMV infection are known to differ according to socioeconomic and geographical settings, this offers a unique opportunity to compare prospective data among Dutch children with a congenital CMV infection to those in a high endemic environment. We will be able to broaden the applicability of our findings and models. By combining our prospective study with the development of a treatment trial and immunological analysis, synergy will be provided to understand infection dynamics and pathogenesis.

Planned activities
- Serological testing of serum samples of the Pienter 2 study.
- Determine from the serological profile the percentage of congenital CMV infections among women.
- Prepare cohort study together with collaborators.
- Preparing study protocol for medial ethical approval.
- In-depth epidemiological data-analysis to study the determinants of susceptibility.
- Development of a realistic age-structured transmission model of CMV infection dynamics.
- Set up of cohort.
- Paediatric, audiological, ophthalmological and cognitive and motor development assessment.
- Mathematical modelling of the dynamics of CMV infections.

Planned products
- CMV serological results will be linked with the existing Pienter 2 database including contact data.
- A database with clinical and immunological outcome data of congenitally CMV infected neonates and controls.
- Mathematical model will be set up to study the dynamics of CMV infection and disease burden in the population with different vaccination strategies.
- Peer reviewed publications.
- PhD thesis including the peer reviewed publications.

Foreseen follow-up
Detailed knowledge on cytomegalovirus with respect to Dutch epidemiology and virology will complement knowledge on in-depth epidemiology, modelling and virology of other early life infections for which one or more (cost)effective interventions might be available. CMV has largely been neglected as public health issue. This proposal enables to generate expertise in this field and to establish a basis for future public health interventions.
We will further be able to contribute to informing the Health Council and Ministry of Health, Welfare and Sport on the health burden and impact of preventive measures of congenital CMV infection. The health council advised in 2007 to extend insight into health burden of CMV. New assignments are therefore highly likely, e.g. to estimate (cost)effectiveness of alternative intervention strategies. The results will contribute to the prospects of including screening on neonatal CMV infection in the existing national neonatal screening programme using dried blood spots.
In addition to national spinoff internationally these data are relevant to inform on the potential of new preventive measures. The results will benefit future

infected children and their families as well as clinicians taking care of these children.
A cohort design enables potential further follow-up after two years of age (findings at one and two years of age are relevant outcome measures already e.g. for hearing loss) with measurements at older age.

Title:	**Environmental risk factors for Q fever**
Project number:	**S/210206**
Project leader:	W. van der Hoek (Wim) (CIb–EPI)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 454,100

Motivation
Since 2007, the Netherlands has been facing annual outbreaks of Q fever, which are unprecedented in the world. Q fever is now considered a major public health problem and has recently led to drastic measures, including large-scale vaccination campaigns of sheep and goats and culling of pregnant goats on infected farms. It is likely that the decline in incidence that was observed in 2010 can be attributed to these interventions. However, even in 2010 the number of Q fever notifications is very high compared to other countries and the causative agent *Coxiella burnetii* is very resilient to a wide range of environmental conditions. Q fever is therefore not expected to disappear from the Netherlands anytime soon. Serious knowledge gaps regarding the transmission of *Coxiella burnetii* still exist. For example, there is epidemiological evidence that people living close to an infected dairy goat farm have a much higher risk for Q fever than people living further away. However, there are also dairy goat farms with Q fever without any human case in the surroundings. Results from an initial study showed that vegetation and wetter soil conditions can also reduce the dispersion of *Coxiella burnetii*. It is, however, unlikely that these are the only environmental factors that determine risk of transmission of Q fever to man. Atmospheric dispersion, depending on fine dust concentrations and wind conditions are critical. Factors that have to be explored in more detail are type of vegetation, combinations of soil types and dustiness, extent of the built environment, animal densities, and prevailing weather conditions.

Aim of the project
The proposed project will develop methods for enhanced surveillance of human Q fever, for detection of animal sources, and for assessing the role of environmental factors in the transmission from animal to man. These methods go beyond the subject of Q fever and can be used for other infectious diseases, especially zoonoses, which have environmental sources and no human-to-human transmission.

Strategic and innovative aspects
The innovative aspect of this project is that routinely collected surveillance data on a notifiable infectious disease are not only interpreted with human epidemiologic methods but also with inputs from veterinary epidemiology and advanced research methodologies from the environmental sciences such as the use of remote sensing, and atmospheric and hydrological modelling. Although focused on Q fever, this combination is expected to provide a model for better understanding of transmission patterns of zoonotic diseases in general. It will add a new dimension to the expertise on epidemiology and microbiology that already exists within RIVM.

Another innovation is the provision of a scientific basis for risk maps and the development of dynamic risk maps in a publicly accessible web environment based on weather data and other environmental factors.

Planned activities
The aim of the project is to fill specific knowledge gaps that exist on transmission of Q fever from infected farms to humans, with special focus on environmental factors.
Specific objectives are:
- To identify environmental factors that determine transmission of Q fever from animal to man.
- To quantify the risk for human infection as a function of environmental factors.
- To develop a method for real time detection of human infectious disease hot spots.
- To develop methods for efficient source detection.
- To compile a risk map of Q fever for the Netherlands.
- To create a dynamic map on a publicly accessible website showing current local and regional transmission risks based on real-time weather data and other environmental factors.
- To perform cost-effectiveness analyses of possible environmental interventions.

Planned products
- Approximately 12 peer reviewed publications.
- Three PhD theses.
- Web based risk map.
- Policy briefs of important findings.
- Risk map of Q fever for the Netherlands.
- GIS (Geographic information systems) tools for interactive mapping and analysis.

Foreseen follow-up
Journal articles will fill important knowledge gaps and will therefore be of benefit to the international scientific community and to professionals involved in emerging zoonotic diseases. Results from the project will make it possible for policymakers and planners to make informed decisions. Health care professionals and the public will be able to use the web tool that will be developed under the project.
Project results will have a strong impact on developing the science on risk and distribution paths of diseases in general and of Q fever in particular. Especially the linkage between epidemiological research and advanced environmental science can be considered as innovative and will result in a better understanding of processes. It can be expected that this type of research approach might open the venue to a new research area.
From a societal point substantial profit can be expected to support decision-making, in particular the current debate on the maximum size and locations of goat and sheep husbandry. The project will give insight in and quantify the potential risks of high animal concentrations close to populated areas. These risks will have to be taken into account for future spatial planning.

Title:	**EU hepscreen**
Project number:	**V/210734/01**
Project leader:	Hahné, mw. drs. S.J.M. (Susan) (CIb/ EPI)
Start:	15-10-2011
End:	31-12-2014
Total SOR-budget:	€ 99.700

Motivation

Chronic viral hepatitis B and C is a major health problem in many European countries. Migrants from endemic areas in particular, are the most affected and underserved population groups. Most European countries have large migrant communities. Often these migrant groups pose important public health challenges, including high prevalence of chronic viral hepatitis B and C. Screening for these two diseases and subsequent treatment of patients can reduce morbidity and mortality to liver disease such as cirrhosis and liver cancer considerably. Because the majority of the disease burden related to chronic hepatitis B and C is found in migrant groups, reduction of the burden of disease will also decrease inequalities in health between migrant and non-migrant groups. The project will describe screening strategies that can be used for different target groups. By using best practices the positive effects on health can be maximized.

The overall objective of the EU Hepscreen project is to assess, describe and communicate to public health professionals the tools and conditions necessary for implementing successful screening programmes for hepatitis B and C among migrants in the European Union.

Central in the project are four pilot studies using different screening strategies. These will be carried out in Spain, England, Scotland and Hungary using systematic, opportunistic and outreach approaches for case detection of chronic hepatitis B and C and targeting different migrant groups.

The RIVM contribution to these pilots will be to coordinate the collection of data that is necessary to assess the cost-effectiveness of the screening pilots in the four pilot sites. This data will subsequently serve as input for subsequent cost-effectiveness analyses.

Aim of the project

The aim of the overall project is to develop tools so that screening of migrants for HBV and HCV infection can be implemented. Screening allows early treatment of 'silent' (i.e. asymptomatic) infections, which reduces the risk of liver disease and death. The aim of the RIVM contribution is to collect the data necessary to assess the cost-effectiveness of the screening pilots in the four pilot sites, for input into subsequent cost-effectiveness assessments.

Strategic and innovative aspects

Although in the Netherlands several HBV and HCV screening pilots for migrants have been carried out, national policy and guidance about this is lacking. Results of economic analyses are an essential component to develop these. Knowledge and data accrued during this project will aid the development of national policy in this area.

Planned activities

- Work package 1, coordination of the project.
- Work package 2, dissemination op the project.
- Work package 3, evaluation of the project.
- Work package 4, screening, treatment, health care and patient management.

- Work package 5, communication to target population and health professionals.
- Work package 6, pilot investigations.
- Work package 7, integration of results and development of a tool kit.

Planned products
- Project website.
- Dissemination products, tools and channels.
- Final product evaluation report.
- Report on the screening and clinical management practices of hepatitis B/C.
- Residential course.
- Webbased information package.
- Report on the results of the pilot studies.
- Input data for cost-effectiveness assessment.
- Tool kit and policy recommendations.
- Technical and financial reports.

Foreseen follow-up
Screening of migrants for HBV and HCV infection allows early treatment of 'silent' (i.e. asymptomatic) infections, which reduces the risk of liver disease and death. Migrants with HBV or HCV are therefore the group that will benefit from this project.
This will be achieved by communicating the results of this project to key stakeholders (policy makers, clinicians). WP five is dedicated to this.

Title:	**Assessing population exposure and immunity to new pandemic norovirus strains**
Project number:	**S/230176**
Project leader:	Prof. dr. M. Koopmans (Marion) (CIb-LIS)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 533,300

Motivation
In the Netherlands, the number of consultations for acute gastro-enteritis (AGE) almost doubled between 1996 and 2006, the number of hospitalizations increased by over 50% and mortality by 20%. Reasons for the increases are not entirely clear, but coincide with emergence of new norovirus variants. Advanced phylodynamic analyses have confirmed that since 2002 the virus population has diverged from the stable equilibrium that one would expect to see for an endemic disease, and that rapid evolution occurs followed by epidemics caused by new variants. It also has become clear that norovirus may cause prolonged or even chronic infection in risk groups, with severe symptoms.

The size of the population at risk for prolonged and severe norovirus infection will grow significantly over the coming years. Therefore, without effective counter measures the impact of noroviruses is likely to increase over time. As a consequence, candidate vaccines, based on virus-like particles, are being developed and have entered phase 3 trials. Here, composition of vaccines is decided based on systematic surveillance done by World Health Organization (WHO) collaborating centres that characterize influenza viruses collected worldwide. For noroviruses, such surveillance does not exist, but RIVM is seen as a reference centre following two European Union (EU) funded projects that ended in 2009.

This proposal aims to work with the global Noronet partners to develop a systematic approach to detection of new norovirus variants. We will develop microarray based serological assays to be able to measure incidence of infection with new variants at the population level in different age groups.

Aim of the project
Changes in this incidence will be studied using microarray based serological methods by comparative testing of serum samples of randomly selected persons from two population serosurveys available at RIVM and from a historic serumbank available in Rotterdam.
Specific objectives are:
- To develop a global collaborative network for exchange of norovirus sequences and strains.
- To use this network to identify new strains with potential for global spread.
- To develop assays for specific measurement of immune responses to the global norovirus variants.
- To do comparative evaluation of seroprevalence of new norovirus variants before and after a 'pandemic' wave (defined as a global epidemic wave).
- To use this data to evaluate the possible role of cross protection.
- To explore the possibility of developing antigenic cartography for noroviruses.

Strategic and innovative aspects
At present, there is no systematic exchange of data on (new) norovirus variants and their spread. Given the rapid succession of pandemic waves of noroviruses in the past eight years, such international comparison of data is timely and needed.
Here, we propose to develop a setup that allows comparative evaluation of the incidence of new norovirus variants against historic strains, using a tool that can easily be exported to other laboratories and countries. Through international collaboration among virologists we will identify which novel strains have the potential for global spread, and subsequently add the relevant antigens to the existing microarray to allow serological measurement of exposure and population impact. This approach is unique in the world, and will be an important basis for discussions on vaccination once norovirus vaccines are brought to the market. Methods used can also be transferred to the clinical laboratories, where norovirus diagnostics have been implemented and the relevance of noroviruses is increasingly recognized. Through collaboration with a project studying norovirus transmission in health care settings, we will evaluate the possible use of serology in supporting control of outbreaks.

Planned activities
- Systematic snapshots of virus diversity in the global noronet collaboration to map diversity of circulating strains.
- Analysis of norovirus genomes for possible B cell epitopes.
- Cloning of selected proteins.
- Preparation and validation of microarrays.
- Serological screening of patients and sera from population-wide serosurveys (third and fourth year; third year measurements, fourth year validation and analyses).

Planned products
- A PhD thesis, including at least four publications in peer reviewed journals.
- The microarrays can be offered to other laboratories at cost price of in the form of collaborative projects.
- The consolidation of a global collaborative laboratory network.
- Our data will be crucial in understanding dynamics of norovirus and the consequences thereof at the population level. This data is what the WHO

needs for the burden of disease studies that are in progress. The WHO has expressed a keen interest in such a study for noroviruses.

Foreseen follow-up
This project will provide insight in the epidemiology of new pandemic norovirus variants, and measure their impact at the population level. This information is crucial for decision-making about the need for control measures. At present, the WHO Food epidemiology reference group is trying to do a global burden of disease estimate and has listed noroviruses as one of their priority candidates. The methods developed will allow comparative multicountry studies of norovirus incidence and thus be of great relevance to this activity. Also, once norovirus vaccines come to the market, this data will be needed to be prepared for the debate on their implementation.

Title:	**Biomarkers for long-term sequels of Q fever**
Project number:	**S/230186**
Project leader:	Dr. D.W. Notermans (Daan) (CIb-LIS)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 999,700

Motivation
Since 2007, the Netherlands are confronted with the largest Q fever outbreak ever described, with over 3500 laboratory confirmed notified cases in three years. Drastic intervention measures have been taken to limit further spread of Q fever, i.e. vaccination of goats, and culling of pregnant goats. However, it is expected that Q fever will remain a significant problem, because *Coxiella burnetii* is a highly resilient organism that is able to survive and persist in the environment for years. As a result, it is expected that it will take a long time for the effect of intervention measures to become apparent. In line with this, a large number of new Q fever cases have been reported in the beginning of 2010 (more than in the same period in 2009).
Presentation of the disease following acute infection is highly variable ranging from asymptomatic seroconversion in about 50% of the individuals, to flu-like symptoms and pneumonia frequently requiring hospitalization. Although infection with *C. burnetii*, the causative agent, is generally considered self-limiting, a number of long-term manifestations with significant health care consequences exist.
Because of the large size of the epidemic, a considerable number of chronic cases and a large number of individuals with chronic fatigue is to be expected the coming years, with potential severe consequences for the affected individuals and high costs for society and the health care system. Moreover, in a small percentage of cases, a chronic infection with life-threatening manifestations such as endocarditis or a vascular infection can occur months to years after the acute infection. The risk of developing serious complications of Q fever cannot be accurately predicted with the current state of the art.
Which host-pathogen and pathogen factors are involved in determining whether a patient will recover from Q fever or will develop chronic sequels of Q fever is not known. In the Netherlands, we now have the unique opportunity to study these factors thoroughly. Insights gained could lead to intervention, for instance through recommendations on follow-up of subgroups of Q fever patients at risk of developing very serious complications.

Aim of the project
Long term sequels occur in a proportion of patients, but which host-pathogen and pathogen factors determine the course of the disease is largely unknown.

Ultimately, we aim to predict the long-term health effects, and to identify targets for intervention.
Specific objectives are:

- To identify host-biomarkers that distinguish patients with chronic sequels of Q fever, from those that recover from infection without sequels.
- To investigate whether *C. burnetii* strains from patients with long-term sequels differ from those found in acute infection, in order to identify pathogen genetic markers.
- To develop a prediction model based on identified host-biomarkers, *C. burnetii* genetic markers combined with clinical data, which can be used to predict the development of long-term health effects of Q fever.
- To build a Q fever network that focuses on host-pathogen interaction in Q fever and the long-term consequences of Q fever for public health.

Strategic and innovative aspects

The innovative nature of the project lies in the fact that the dynamic interaction between both host- and pathogen factors involved in determining the disease course will be studied.
Analysis of whole genome sequencing is a fast developing field which nowadays is feasible and applicable for investigating field isolates. CIb is currently investing in novel bio-informatics tools to analyse the data that are generated. CIb is one of the few laboratories in the Netherlands, with experience and expertise in culturing human pathogens at the BSL3 (biosafety level) and even at BSL4.
The proposal is highly strategic because it aims to integrate clinical knowledge with laboratory research. In addition, various (inter)national experts that each provide their own expertise to the project, will participate as external advisors which gives the opportunity to link all available knowledge on long-term health effects of Q fever that is generated in the field. This will provide us with a broad knowledge network that will enable us to work towards more efficient intervention. The insights gained from the proposed studies can also be made applicable for other (zoonotic) infectious diseases in the future.

Planned activities

- Identification of host-biomarkers for long-term sequels. The three approaches to identify biomarkers of chronic Q fever are:
  - Analysis of serum markers expressed during chronic disease.
  - Whole blood responses of chronic vs non-chronic patients.
  - Host genetic markers of chronic sequels.

- Identification of pathogen-genetic markers for long-term sequels. In parallel genetic factors of the pathogen will be studied. In murine models isolates from acute infection induce stronger inflammatory responses than isolates from chronic Q fever, indicating that virulence of the pathogen may play a role:
  - Whole genome sequencing.
  - Evaluation of candidate genetic markers.

- Develop a model to predict the development of long-term sequels.
- Build a Q fever knowledge network.

Planned products

- 'Vital knowledge' of the factors that determine the differences in long-term effects of Q fever, therefore helping in better identifying populations at risk and strategies for interventions.
- Peer reviewed publications.
- Ultimately, these data will be translated towards strategies for intervention in development of long-term sequels of Q fever.

Foreseen follow-up
The Dutch Ministry of Health, Welfare and Sport (VWS) and the Ministry of Economic Affairs, Agriculture and Innovation (EL&I) have designated Q fever as an urgent health problem that needs to be controlled. At the moment, funding from both ministries is mainly aimed at putting a halt to the Q fever epidemic and at the short-term problems that have arisen from this epidemic. However, as stated above, the long-term health problems associated with Q fever are just starting to reveal and a significant part has yet to come. Therefore, knowledge on this aspect of the disease is crucial for RIVM, in order to provide both Ministries with adequate advice in the future.

The results of this study will lead to the identification of critical determinants of chronic sequels of Q fever. A better understanding of the pathogenesis of the different forms of Q fever and possible better ways of identifying patients at risk for a more severe disease course may, in the future, guide management of disease. By combining host biomarkers and *C. burnetii* genetic markers with clinical data we aim to predict patients at high risk of developing serious, chronic sequels of Q fever.
In addition, it is becoming more and more apparent that successful interventions in infectious diseases depend on knowledge on both the pathogen and the host-response. Therefore, the knowledge gained within this project can be used as input for other future and ongoing host-pathogen interaction research at RIVM aimed at vaccination, treatment or other types of intervention.

Title:	**Proteomic profiling of XDR TB**
Project number:	**S/230196**
Project leader:	Dr. M.R. Klein (Michel) (CIb-LIS)
Start:	01-07-2011
End:	30-06-2015
Total SOR-budget:	€ 1,285,000

Motivation
Each year, 10 million people contract tuberculosis (TB) and 2 million die as a result of the disease. An estimated 2 billion individuals have been exposed to Mycobacterium tuberculosis (MTB) and carry the infection in its latent form. To control and eventually eradicate TB, we will need better diagnostics tools, innovative biomarkers, new drugs, correlates of protective immunity and novel vaccines. A promising innovative approach is to target host processes in order to control MTB. Because of the fact that XDR (extensive drug-resistant) MTB strains can cause a lethal infection in humans, have a great potential to spread through the community, and for which there is currently no vaccine or treatment available, we will pursue the work with live XDR MTB strains in the BSL4 (biosafety level) laboratory. Currently, the dynamic and temporal changes in the host and mycobacterial proteomes during infection and treatment have not been studied extensively. The aim of this project is to study both the mycobacterial and host responses to infection and subsequent treatment, in order to reveal potential targets for future diagnostics and interventions.

Aim of the project
The overall aim is to profile the dynamics of host and bacterial responses to infection with XDR MTB strains and to study the impact of anti-TB drugs as well as inhibitors of host intracellular targets. To achieve this we will use an innovative approach for quantitative proteomics profiling. This will allow us to gain insight into mechanisms of drug-resistance, host-pathogen interactions and identify new targets and/or biomarkers for diagnostics, vaccination and treatment of TB.

Specific objectives:
- To select and grow batches of representative MTB strains with a spectrum of antibiotic resistance and mycobacterial genotypes and to set up and optimize (large-scale) *in vitro* infection models with human cell-lines susceptible to infection with mycobacteria.
- To profile temporal stress responses of model biological agents, (XDR) MTB strains and host cells to new combinations of anti-microbial drugs directed at mycobacterial targets, and inhibitors of host intracellular targets.

Strategic and innovative aspects
This project concerns scientific research and aims to explore new fields. The combination of well-defined MTB isolates, a unique high-containment facility in the Netherlands, and the application of a powerful quantitative proteomics platform to study the host and mycobacterial stress responses to infection and treatment, is a comprehensive and novel approach. At this moment there is only one publication on proteomic profiling of host cells in response to MTB. We propose to perform quantitative proteomic profiling of intracellular mycobacteria, which is highly innovative and has not been explored before.

Planned activities
- Preparation of all experimental activities: organize our research materials (MTB strains, anti-TB drugs and host-cell inhibitors, other reagents, cell-lines and samples and set up our project's administration, including a database for the proteomics studies.
- Select from our unique collection of MTB strains and other mycobacteria, with varying levels of drug-resistance and representing the major genotypes that are presently circulating or emerging worldwide.
- Culturing selected MTB strains and cryopreserve aliquots for our experiments. Validating that the heat inactivation procedures are effective in killing all viable mycobacteria in the samples.
- Determination of the host response to drug treatment without infection. Titration experiments will be performed with (novel) anti-TB drugs and cellular inhibitors to determine the cytotoxic effects of drugs on cell-lines. Secondly, mycobacterial response to drug treatment will be assessed.
- Setting up and optimizing (large-scale) in vitro infection experiments of cell-lines susceptible to infection with mycobacteria.
- Profiling the host response to infection.
- Profiling the host response to infection and drug-treatment.
- Profiling intracellular mycobacteria and their adaptive response to infection.
- Profiling intracellular mycobacteria and their stress response to infection and drug-treatment (known and novel anti-TB drugs or antibiotics and host cell inhibitors.

To study the response to infection and treatment, we will infect human cell-lines as well as primary cell-cultures with well-defined XDR-MTB strains and other mycobacteria and subject them to toxic/inhibitory effects of (novel) anti-microbial drugs directed at bacterial or host targets. The lysates will then be subjected to quantitative proteomics. This method is a very powerful approach to perform large-scale kinetic analysis of proteomes and post-translational modifications.

Planned products
- A number of peer reviewed scientific publications.
- At least one PhD thesis.

Foreseen follow-up
This project will allow us to gain expertise, technical capacity and build our knowledge-base in the area of high-risk human pathogens and mechanisms of

antibiotic resistance, which most definitively will strengthen our (inter)national position, as leading centre for TB diagnostics and molecular epidemiology.
Our technical setting – infection of human cells with mycobacteria and quantitative mass spectrometry/proteomics – will allow us to also study immunological questions; e.g. identification of the mycobacterial ligandome that is presented and seen by the host immune system. The study of the ligandome and relevant epitopes is one of the core activities of the MS-group (Multiple sclerosis) at Leiden University (LUMC). In addition, the proteomics approach explored here can also be applied to study the dynamics of other microbial infections relevant to public health.
The data that we generate as part of proteomics profiling will allow us to formulate new hypotheses for future studies. We are therefore confident that the successful execution of this project will also give us a cutting edge for new assignments ('kennisvragen') and future applications for competitive external funding.
Despite the fact that we expect that our project will contribute to better and improved tools for diagnostics and treatment of TB in the future, because of the hypothesis-generating nature of this project, this aspect is clearly beyond the immediate scope of our project.

Title:	**Antivirals against Enteroviruses**
Project number:	**S/230206**
Project leader:	Avoort, dhr. dr. H.G.A.M. van der (Harrie) (CIb/LIS/VIR)
Start:	01-09-2011
End:	31-08-2012
Total SOR-budget:	€ 200.000

Motivation
The poliovirus is a major causative agent of acute flaccid paralysis in children and thus forms a major threat for human health. To eradicate polio globally, enormous investments [~7 billion dollar] were made by vaccination with the inactivated and life attenuated oral poliovirus vaccines (OPV). The use of OPV strains is not without risks. Upon replication in the human intestinal tract, the sites of attenuation may mutate, which results in reversion of the vaccine strain, able to cause (outbreaks of) vaccine associated paralytic poliomyelitis. To prevent emergence of such viruses in the final stages of eradication, IPV will be introduced where possible and three years after eradication of the disease vaccination with OPV will be stopped everywhere in the world.

Antiviral drugs against poliovirus will be urgently needed, to prevent reintroduction of neurovirulent polioviruses in the community. This is done by treating immunocompromised patients with chronic shedding of vaccine strains, or persons who are accidentally infected with wild type poliovirus during the IPV production process.

Currently, there is, however, no approved antiviral therapy at hand for the treatment of poliovirus infections. The Taskforce for Global Health (in collaboration with Atlanta CDC and the RIVM) has recently initiated a study on the antiviral activity of several novel and promising drug candidates in human poliovirus infection. Part of the SOR budget will be used to facilitate the study by making all tests required for this large scale study operational before the time of start.

The RIVM has the task of coordinating national enterovirus (including polioviruses) surveillance in the Netherlands. For the RIVM it will be of utmost importance to embed expertise on the pro's and con's of applying anti-enterovirus drugs, such as the potential emergence of drug resistant viruses and kinetics of drug-virus interaction in the environment. The major part of the SOR budget will therefore be used to gain expertise and knowledge on development of drug resistance (does it occur? how fast? how to monitor emergence of such viruses? do we need combined therapies?). This will be gained by research collaborations with Atlanta CDC, Rega Institute and NCMLS. These institutes are at the forefront of studying molecule inhibitors and drug development and have some useful in house models to monitor and evaluate development of drug resistance. Additionally, they have expertise on relating drug resistant phenotypes to certain changes in the viral genomes of drug resistant variants. This knowledge is of importance to study natural occurrence of such mutations in circulating enteroviruses and development of screening methods for identification of drug resistant viruses once the drugs are applied.

Aim of the project

The aim of the project is to embed knowledge at the RIVM on the development of anti-enterovirus drugs and the consequences of using these drugs in the field for public health and the national enterovirus surveillance system. The goals will be achieved by:

- Participating in a study initiated by the Task Force for Global Health on the efficacy of novel anti-polio drugs in human infection (The Polio Antivirals Project). Part of the SOR-budget will be used to make virological and immunological assays operational before the start of this study.
- Translation of findings into methods suitable for application in the RIVM and the enterovirus typenet laboratory network.
- Development of a long term collaboration of RIVM with CDC Atlanta, Rega Institute, and NCMLS to link to state-of-the art expertise in the development of antivirals.

Strategic and innovative aspects

By participating in the Polio Antivirals Project and building up strong collaborations with institutes active in the field of antiviral drugs, the RIVM will be positioned at the frontline of these new developments and will built up important knowledge on the currently unknown consequences of using these drugs in the field, such as resistance development, and methods to monitor resistance development. The project proposed will help to prepare the RIVM for the future, and to gain the necessary expertise for the future of enterovirus surveillance.

Planned activities

Studies conducted as part of the Polio Antivirals Project at the RIVM, will start in November 2011. From September 2011 until that time, virological and immunological tests that will be used during this upcoming project will be made operational.
Additionally working visits to CDC Atlanta, Rega Institute and NCMLS will be planned to get acquainted with evaluation and monitoring of development of drug resistance and explaining the resistant phenotype at the genetic level. Finally, scientific findings will be translated to a public health related context.

Planned products

Products planned for the fortcoming years are:

- Methods for screening of poliovirus/non-polio enterovirus isolates for antiviral resistance (operational at the RIVM).
- A microarray-based method for assessing antibody profiles to poliovirus, and an operational enterovirus molecular laboratory surveillance network.
- Scientific findings obtained by the Polio Antiviral Project, using these methods, and additional studies on development of drug resistant enteroviruses will be translated to applications in the public health context.
- Results obtained from the Polio Antiviral Project and extended studies will be presented at national and international meetings on antiviral drug development and public health and will be published in leading peer-reviewed international journals in the field.

Foreseen follow-up

Antiviral drugs are very likely going to be applied to achieve and retain total elimination of poliovirus and to threat severe infections with other enteroviruses. For that reason it will be of utmost importance that the RIVM expands its current expertise on enteroviruses and polio eradication with new expertise from the field of antiviral drugs and that the institute is well informed on and able to study the consequences of using these drugs for public health and current enterovirus surveillance activities. Participation in the Polio Drug Project and development of a solid, long-term collaboration with leading, international institutes in this field of research will be beneficial for this. In addition, successful accomplishment of the Polio Antiviral Project a will be beneficial for the recognition of the RIVM as an experienced lab in enterovirus research. This will benefit involvement of the RIVM in future, external projects.

Title:	**Vaccination and pathogen escape (vacscape)**
Project number:	**S/230456**
Project leader:	Prof. dr. F.R. Mooi (Frits) (CIb-LIS)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 527,456

Motivation

Widespread vaccination of children was successful in significantly reducing pertussis morbidity and mortality. However, despite vaccination, *Bortedella pertussis* has persisted and has become the most prevalent vaccine-preventable disease in developed countries. We were first to provide evidence that adaptation of *B. pertussis* has played an important role in the persistence and resurgence of pertussis. More recently, we identified a novel lineage comprised of (so-called) P3 strains which produce more pertussis toxin (Ptx) and which are more virulent in humans. The changes observed in *B. pertussis* populations occurred in the whole cell vaccine (WCV) era. In most western countries, WCVs have been replaced by acellular vaccines (ACVs). The immune response induced by the two types of vaccines is qualitatively and quantitatively different. The major question is: how will these differences affect the *B. pertussis* population and the pertussis burden? WCVs induce a broad immune response, but with relatively low titres, whereas ACVs induce higher titres against only a few antigens (i.e. a narrow immune response). Theory suggests that a change from a broad to a narrow immune response will favour the emergence of escape variants. Indeed in several countries such variants, which do not produce one or more vaccine components, have been identified. In this project these so-called ACV-knockout mutants will be characterized sequencing their genomes and by proteomic analyses and the information will be linked to changes in virulence.

Aim of the project
In general terms, the project focuses on the arms race between human intervention (vaccination) and pathogen response. Ultimately, the goal is to translate the obtained insights into public health measures to reduce the pertussis burden. More specifically, the project aims to determine the public health relevance of the emergence of strains which do not produce one or more acellular vaccine components (referred to as ACV-ko (knockout) mutants). We will assess the prevalence of ACV-ko mutants in Sweden and the Netherlands. Further, the ACV-ko mutants will be characterized by sequencing their genomes and by proteomic analyses. By linking strains with patient data we aim to investigate whether the ACV-ko strains changed in virulence.

Strategic and innovative aspects
The project is innovative, as it replaces classical approaches for strain surveillance (based on e.g. pulsed-field gel electrophoresis and sequencing of a limited number of genes) with a holistic approach, based on high throughput phenotypic screening, comparative genomics, proteomics and bioinformatics. Further, the project explores uncharted areas, as switching from a vaccine which induces broad immunity to one which induces narrow immunity is unprecedented. Importantly, the insights obtained will be relevant for other infectious diseases which are controlled by ACVs, particularly those with a limited number of antigens.

Planned activities
- Strain collections and epidemiological data. Our Swedish sister institute has a unique collection of Swedish strains with linked temporal, geographic and patient data. The patient data includes vaccination status, age, clinical symptoms and duration of hospital stay. This linkage with patient data allows us to investigate changes in virulence of strains. A large Dutch strain collection with linked spatial and temporal data is available at the RIVM. Although clinical data is not available for the Dutch strains, the age of the patient is known.
- Vaccination histories. After a vaccine-free period of 17 years, vaccination with ACVs was reintroduced in Sweden in 1996. This history makes Sweden unique and allows us to study the effect of ACVs on the evolution of *B. pertussis* without confounding factors caused by the switch from WCV to ACV. Dutch strains from the ACV-free period (isolated before 2002) will be compared with Swedish strains to assess the effect of vaccine type on the bacterial population.
- Whole genome sequencing will be performed with Illumina technology, complemented with 454-sequencing for a limited number of strains.
- Phylogenetic analyses will be based on single nucleotide polymorphisms (SNPs). We have identified approximately 900 SNPs by whole genome sequencing of 60 *B. pertussis* strains.
- A Luminex assay will be used to screen large numbers of strains for the (absence of) expression of antigens used in ACVs. The advantage of the luminex assay (compared to e.g. an, enzyme linked immuno sorbent assay (ELISA)is that it is less laborious as multiple antigens can be tested in a single (sandwich) assay.
- Proteomics will be performed for phenotypic analyses of a limited number of strains.

Planned products
- Approximately five peer reviewed publications.
- PhD thesis.

Foreseen follow-up
In a sense, the project looks into the future by studying *B. pertussis* populations in a country where ACVs have been used much longer than in the Netherlands.

This will allow us to anticipate changes in the Dutch pertussis population and suggest appropriate interventions, which may lead to new assignments. E.g. the widespread emergence of strains not expressing one or more vaccine components may necessitate the use (and evaluation) of ACVs containing more than three pertussis components. In the long run, improved vaccines may be required, based on more stable surface components. The project provides the technology and may reveal the necessity (and thus lead to assignments) for similar studies focused on pathogens which are controlled by other vaccines which target only one or a few antigens such as MenC and Hib vaccines. Finally, the project will highlight the importance of strain surveillance, a core activity of CIb.

Title:	**Control of tick-borne diseases: shooting the messenger**
Project number:	**S/330136**
Project leader:	Dr. H. Sprong (Hein) (CIb-LZO)
Start:	01-01-2010
End:	31-12-2014
Total SOR-budget:	€ 965,800

Motivation

How to maintain a sustainable nature while minimizing the threats of zoonotic diseases from wild and domestic fauna within rural and urban environments? Changes in landscape design, climate and human behaviour pose unexpected and (re)emerging threats of zoonotic diseases. Our environment is subject to continuous changes, mostly by human intervention. Expanding and linking areas for wildlife to create ecological networks in the Netherlands and across Europe are not only beneficial for biodiversity and wildlife, but also for the microorganisms they carry. A prominent case is Lyme borreliosis, which is becoming a major public health concern; the number of tick bites and patients with Lyme disease in the Netherlands has increased dramatically in the past decade The same tick species transmitting the aetiologic agents of Lyme disease also serves as vector of pathogens causing tick-borne encephalitis, babesiosis, several forms of rickettsioses and anaplasmoses, and potentially also the causative agent of Q fever. Incidences and public health risks of tick-borne diseases other than Lyme are largely unknown.

A vaccine against tick-borne encephalitis virus is available, but a vaccine against the European variants of Lyme borreliosis is nonexistent. The control of tick-borne diseases is predominantly based on prevention of tick bites by education, but has not resulted in even a stabilization of the incidence of Lyme disease in the Netherlands. Except for a brief campaign to reduce Lyme disease in the former Soviet Union through widespread application of detrimental insecticides, success stories in the fight against tick-borne diseases in Europe are lacking. A key question is: What has caused the increase of Lyme disease in the Netherlands? We hypothesize that the number, size and capacity of tick-suitable habitats have steadily increased in the past 40 years. Furthermore, the unlimited increase in the abundance and local density of roe deer Capreolus capreolus, one of the major hosts for adult ticks, has resulted in an increased reproductive capacity for ticks. There is no evidence that other factors such as human behaviour (e.g. outdoor recreation) or the infection rate of ticks have changed dramatically over the last decades.

In the United States, successful control strategies have been developed that focus on the killing of American tick species on white-tailed deer, which are important for feeding and mating of adult ticks. Devices have been developed

that bring large grazers in contact with acaricides that will kill ticks present on the host. These experiments have resulted in tick reductions of more than 65% in a period of 3-4 years. Other promising methods include the use of biological agents for the control of larval and nymphal ticks. These strategies are highly promising and desirable. However, to apply any method of tick control, these first need to be developed and evaluated for the Dutch/West European situation.

Aim of the project
Our long-term aim is to minimize the risk of infectious diseases from wild and domestic fauna. The aim of this project is to develop effective and sustainable methods for the control of Ixodes ricinus populations in order to decrease the current risk of Lyme disease. The reduction of tick densities will result in fewer tick-bites, and consequently to a lower incidence of Lyme disease.
Specific objectives are:

- Determine whether the hazard for Lyme disease (i.e. density/activity of infected ticks) can be reduced via the reduction of reproductive and/or feeding capacity of ticks.
- Identification of the feeding hosts of adult Ixodes ricinus ticks and their relative contribution to tick mating in the Netherlands.
- Identification of the feeding hosts of the larvae and nymphs of Ixodes ricinus ticks and their relative contribution to tick feeding in the Netherlands.
- Identification of the competent/incompetent and reservoir/dilution hosts of Borrelia burgdorferi genospecies and Ixodes ricinus ticks and their relative contribution to the infection rate of Ixodes ricinus ticks.
- Implementation and validation of tools to assess quantitatively the risk (factors) of Lyme disease. These tools enable us to evaluate the risk of Lyme disease upon the application of the combination of different tick control strategies, and also upon climatological and ecological changes.

Strategic and innovative aspects
The ecology of zoonotic diseases from wildlife and their consequences for the human population and the possibilities for intervention deserves renewed awareness from policymakers, public health professionals and from the public. Tools that can predict the effect on the risks of zoonotic diseases upon man-made changes in the environment, including those from control measures, offer a distinct advantage for a public health institute.

RIVM's Laboratory for zoonoses and environmental microbiology holds a unique position in the Netherlands as it functions at the interface of environment and public health. This full collaboration between Wageningen University and the RIVM with both scientific and substantial financial input from both parties will greatly enhance the interaction and future collaborations. A long-term collaboration and interaction between 'ecology' and 'infectious diseases' is of strategic importance and will be beneficial for tackling other zoonotic diseases related to wildlife and vectors.

Planned activities

- Selection of control areas and areas of intervention. Once this proposal is granted, we will immediately apply for (temporal) approval of the selective use of several acaricides, including Metarhizium anisopliae, and select for corresponding devices for the application on wildlife.
- Reduction of breeding and/or feeding capacity of ticks. Several strategies to reduce ticks densities will be investigated.
- Research on community ecology of ticks and tick-borne diseases.
- Research on population dynamics of tick and tick-borne diseases.
- Development of models for risk assessment and evaluation of control strategies.
- Integration of data and communication.

Planned products
- Science-based, practical and effective application(s) to control ticks and tick-borne diseases by the reduction of tick populations.
- A set of tools to quantitatively assess the risk (factors) of Lyme diseases.
- Two PhD theses.
- Publications in peer reviewed journals.

Foreseen follow-up
Effective control measures to tackle tick-bites and tick borne diseases will mostly be beneficial for the health status of the human population, but also of wildlife and domestic animals, as their incidence of tick borne diseases will probably decrease. If successful, this SOR proposal offers new and practical means for policymakers, nature conservation agencies (e.g. Staatsbosbeheer, Natuurmonumenten, Provinciale Landschappen) to control the number of ticks in high risk and recreational areas. Our acquired experience in tick control will be necessary for further successful implementation.

The models and strategies developed could be deployed by the Ministry of Health, Welfare and Sport and the Ministry of Economic Affairs, Agriculture and Innovation as a prototype for new assignments to RIVM regarding control of many other zoonoses from wild and domestic fauna in rural and urban environment. The results of this project will be of great interest for other European countries, which also seek novel ways to control and tackle tick-borne diseases.

Title:	**ESBL genes on fresh produce**
Project number:	**S/330156**
Project leader:	Dr. H. Blaak (Hetty) (CIb-LZO)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 913,470

Motivation.
Because of the use of antibiotics in human health care and the large amounts of antibiotics used in animal husbandry, the prevalence of antibiotic resistant bacteria is steadily increasing. Of special concern for public health is the observed increase of bacteria that have acquired the capacity to produce extended spectrum beta-lactamases (ESBLs) and carbapenemases. Infections with ESBL and carbapenemase producing bacteria are difficult to treat, because they display resistance to a broad range of beta-lactam antibiotics, including 3rd and 4th generation cephaloporins and carbapenems. ESBL and carbapenemase producing bacteria are often *Escherichia coli* and *Klebsiella*, intestinal commensals and opportunistic pathogens. These bacteria are not only abundant in humans but also in livestock and in the aquatic environment.
The environment is a repository of antibiotic resistance (AR) genes and resistant bacteria originating from different, animal and human, sources. Compared with exposure to antibiotic resistance through direct contact with human or animal carriers of antibiotic resistance, the environment may present additional risks. Firstly, once in the environment, bacteria may exchange AR-genes with each other or with the environmental microbial population through horizontal gene transfer. Secondly, the environment is a source of novel AR-genes that are carried by soil bacteria, independent of antibiotic use in animals and humans. One relevant route of exposure to AR-genes and resistant bacteria present in the environment is via feed/food that has been grown in contaminated soil or irrigated with contaminated surface- or ground water. Fresh produce is of special public health relevance as it is often consumed raw, and consumption of this

type of food is increasing. However, far less information is available on fresh produce as a transmission route of antibiotic resistance compared to products of animal origin. Fresh produce can be contaminated with bacteria carrying ESBL genes. In this project the presence and origin of ESBL and carbapenemase genes on fresh produce will be explored using genomic based techniques.

Aim of the project
The aim is to quantify the exposure of humans to ESBL and carbapenemase producing bacteria and ESBL and carbapenemase genes through the consumption of fresh produce and associated public health effects. Specific objectives:

- To determine the prevalence of ESBL and carbapenemase genes on fresh produce using cultivation approaches and cultivation-free metagenomics, and to establish their phylogenetic relationship with genes in soil and irrigation water, identified using the same methods.
- To establish the relationship of ESBL and carbapenemase genes on fresh produce and in environmental samples with ESBL and carbapenemase genes found in clinical and veterinary bacterial isolates.
- To determine the contribution of natural and anthropogenic sources to the ESBL and carbapenemase gene load found on fresh produce.
- To quantify human exposure to ESBL and carbapenemase genes and ESBL and carbapenemase producing bacteria due to consumption of fresh produce and to assess the public health effects of this exposure, using Antimicrobial Resistance Risk Assessment (ARRA).

Strategic and innovative aspects
The metagenomic approach to evaluate the exposure of the human population to AR genes via fresh produce and the agricultural environment is one aspect of the innovative nature of this project. In addition, the metagenomic approach will facilitate the discovery of ancestor and novel ESBL genes within the environment.
Results from this study will give insight in the relevance of fresh produce as transmission route of antibiotic resistance relative to food of animal origin that has been studied in more detail. Depending on the results, actions to reduce risks of exposure to antibiotic resistance through fresh produce may appear to be necessary or not. Conceivable intervention strategies might for instance be the implementation of standards for irrigation water quality and protection of irrigation water sources, or restricted use or treatment of animal manure.
ARRA is a new application of risk assessment that is closely related to quantitative microbiological risk assessment (QMRA). ARRA focuses on resistance determinants (genes) as hazardous agents rather than on specific (pathogenic) bacteria, requiring additional challenges like modelling of resistance-transfer in exposure assessments and dose-response relations.

Planned activities

- Collecting fresh produce, soil and irrigation water samples at agricultural sites.
- Determining the prevalence of ESBL and carbapenemase producing bacteria by enumeration of total gram-negative bacteria (GNB), and GNB resistant to cefotaxime or ceftazidime (cephalosporins), or ertapenem (carbapenem) using selective plates. Resistant isolates will be stored and identified using 16S sequencing.
- Analysis of ESBL and carbapenemase resistomes by cultivation-free methods.
- Sampling and analyses of potential contamination sources of irrigation water and soil, such as manure and effluents of nearby waste water treatment plants.
- Sequencing and phylogenetic analysis of ESBL and carbapenemase genes that have been derived from different types of samples, from total DNA as

well as bacterial isolates. Analysis of size and type of plasmids carrying the ESBL and carbapenemase genes from bacterial isolates from the different samples.
- Comparison of ESBL and carbapenemase genes and plasmids found in environmental samples and on fresh produce with those from veterinary bacterial isolates, and human bacterial isolates.
- Construction of DNA libraries for functional metagenomics for a selection of samples (based on results gathered so far), to discover novel ESBL genes.
- Developing a risk characterization of ESBL producing bacteria and ESBL genes present on fresh produce, to estimate the public health effects of exposure to ESBL and carbapenemase producing bacteria and ESBL and carbapenemase genes.
- Characterization by sequencing of cefotaxime, ceftazidime and ertapenem resistant clones found in the functional metagenomic library. If novel ESBL genes are found using functional metagenomic analysis, human and veterinary isolates of different origin as well as soil bacteria will be screened for the presence of these genes.

Planned products
- Knowledge concerning the prevalence of natural and anthropogenic ESBL and carbapenemase genes in soil, different types of irrigation water and on fresh produce.
- Identification of novel ESBL and carbapenemase genes that may pose a threat in the near future
- Knowledge on and experience with metagenomics and additional molecular tools to detect and characterize ESBL and carbapenemase genes in different matrices.
- Knowledge on modelling of public health impact due to exposure to AR-bacteria and AR-genes.
- Six peer reviewed publications.

Foreseen follow-up
The study will demonstrate whether consumption of fresh produce contributes to the spread of ESBL and carbapenemase genes and therewith to the problems caused in the clinic by bacteria carrying these genes. The results will identify contamination sources and will therefore serve as a stepping stone for development of intervention strategies. If results indicate that mitigation is necessary, both public and policymakers will benefit. Independent of the magnitude of the risk of human exposure through fresh produce, the RIVM will profit through publications, knowledge on metagenomic analysis, and new or tightened partnerships.

Title:	**Biotracer, extension 2011**
Project number:	**V/330524/01/BT**
Project leader:	Pielaat, mw. dr. ing. A. (Annemarie) (Cib/ LZO)
Start:	01-11-2011
End:	31-12-2011
Total SOR-budget:	€ 202.400

Motivation
The extension period for the biotracer-IP project was approved by the EU committee for dissemination and publication purposes.
- Dissemination of Biotracer results relating to the pork supply chain at Safepork 2011. This dissemination activity at the international conference SafePork 2011 in Maastricht is a unique opportunity to present our results on Tracing Salmonella in the Pork chain in a Workshop.

- Inclusion of the results of a cross-contamination experiment in the Salmonella in the pork model and dissemination. Additional sampling at the Vion slaughter house gives an unique opportunity to validate the model developed during the 4 years research in Biotracer. Validating models is an often missing part in any Risk Analysis.
- Towards the integration of molecular data in tracing models. This extension tasks gives us the opportunity to publish an overview of our 4 years research work.

Aim of the project

- Dissemination of Biotracer results relating to the pork supply chain at Safepork 2011. By hosting a workshop all results from biotracer from the pork and feed chain relating to pigs and pork can be disseminated. Creating funds will make it financially possible for the Biotracer members and, especially, other researchers outside the project to attend this meeting. This meeting will be an opportunity for the Biotracer partners to update the progress and new findings and renew their contacts.
- Inclusion of the results of a cross-contamination experiment in the Salmonella in the pork model and dissemination. A sensitivity analysis of the biotracing model, concludes that the transfer rates to and from stainless steel are uncertain, yet important, parameters in the biotracing model, limiting the capacity of the model to conduct a biotrace. Therefore an experiment is done to generate data about cross-contamination in the slaughterhouse. Inclusion of these data into the model will increase its discriminative power, making the model a valuable tool for industrial use. As an extension activity, we propose to implement the generated data into the biotracing model. The results of the cross-contamination experiment and the improved biotracing results of the model will be published in an article. J. Smid will incorporate this article to complete his PhD thesis.
- Towards the integration of molecular data in tracing models. Complete this paper with the above suggestions to come to a general paper which discusses the status of the integration of molecular data in tracing models. This paper will form the basis for future biotracer spin-off projects in which molecular tools will be used as an additional source of information in the food safety risk assessment domain.

Strategic and innovative aspects

Strategy is to disseminate our four years research work on Tracing salmonella in the Pork Chain to a larger public than in the Biotracer project alone. The innovative aspects of the research (use of Bayesian approaches and molecular data for tracing) will be presented during a workshop and in international peer reviewed papers.

Planned activities

- Dissemination of Biotracer results relating to the pork supply chain at Safepork 2011. The Safepork organisation will be asked to give a platform for dissemination after approval of the project. Commitment has already been given by the organisation committee (june 2010). A workshop or breakout session, depending on the framework programme of the conference, will be planned (November 2010). The Biotracer partners will be invited to submit abstracts for the conference (January 2011).
- Inclusion of the results of a cross-contamination experiment in the Salmonella in the pork model and dissemination
  - Results cross-contamination experiment and description of laboratory procedures used for estimating the cross-contamination parameters: M.48.
  - Results improved biotracing model of Salmonella in pork: M.51.
  - Draft of manuscript describing the results of these experiments: M.51.

- Towards the integration of molecular data in tracing models. RIVM will take the lead in finishing this paper. Of course will the partners who are actively involved in this process be recognised as contributing author. RIVM will
  - Gather and process all relevant documents as produced within the consortium (M49-51)
  - Produce a new version of the paper, circulate within the authors of the MS until the final version can be submitted (M52-54)

Planned products

- Dissemination of Biotracer results relating to the pork supply chain at Safepork 2011. Report with number of Biotracer partners attending the meeting, the number of posters and oral presentations, number of attendees at Biotracer workshop and the results presented at this workshop. See www.biotracer.org
- Inclusion of the results of a cross-contamination experiment in the Salmonella in the pork model and dissemination. The final article will be completed by the end of June 2011. J. Smid et al, 'Cross-contamination of Salmonella in the pork slaughter chain', submitted to IJFM, June 2011.
- Towards the integration of molecular data in tracing models. The final article will be completed and submitted as international peer reviewed paper by the end of June 2011. A. Pielaat et. al, 'Food chain microbial contaminations: Towards the integration of molecular data in tracing models'.

Foreseen follow-up

Scientific world, stakeholders, industry and governmental institutes will profit from our work.
A follow-up project has already been introduced by Program 5 of the ministry of EL&I "5.2.18 Salmonella varkensketen". In addition, the results of this project will be integrated in a recently awarded Tender by EFSA on "Development of a user-friendly interface version of the QMRA model for Salmonella in pigs developed under grant agreement FP/EFSA/BIOHAZ/2007/01"
We are continuously looking for new opportunities in building further on our developed knowledge in (inter)national projects

Title:	**SUSCLEAN**
Project number:	**V/330664/01**
Project leader:	Franz, dhr. dr. E. (Eelco) (Cib/ LZO)
Start:	01-01-2012
End:	31-12-2014
Total SOR-budget:	€ 299.900

Motivation

The market of ready-to-use minimally-processed vegetables (MPV), has grown rapidly over the recent decades as a result of an increased consumer demand for healthy but easy-to-use fresh foods. Especially consumption of fresh-cut lettuce due to their use in prepared salads was cause of the growth. Parallel, outbreaks of infectious disease related to MPV have increased in the last decade as well. Fresh-cut fruits and vegetables are increasingly considered as possible vehicles of foodborne pathogens by scientific and commercial stakeholders in Europe. Contamination can occur during primary production or by cross-contamination during processing. The recent problems with ESBL-producing bacteria on vegetables and vegetable associated outbreaks of disease like the German EHEC outbreak stresses the importance of controlling the microbial safety of fresh produce. The German EHEC outbreak showed that a microbial

safety crisis associated with fresh produce can result in large public health and political/economic consequences.
Chlorine has been widely used to decontaminate fruits and vegetables in the fresh-cut industry in order to reduce the load of spoilage organisms (to increase shelf-life) and pathogens. However, the association of chlorine with the possible formation of carcinogenic chlorinated compounds in water has called into question the use of chlorine in food processing. Moreover, organohalogen compounds, such as chlorine, are included in the indicative list of the Directive on Industrial Emissions as major pollutants for water emissions and possess carcinogenic or mutagenic properties. The extensive use of water in the MPV washing steps to reduce microbial contaminations also contributes to increased wastewater load. The MPV processes raises therefore health, economic and environmental issues. In addition, current decontamination techniques (chlorination) that do not affect the integrity of food show limited efficiency in reducing pathogen levels as enteric pathogenic viruses
Consequently there is a real need to find alternative efficient decontamination treatments whilst preserving MPV freshness, quality and safety along with the shelf life of the product. The other challenge for the MPV food industry is the minimization of water consumption and wastewater discharge rates. The project will tackle all these requirements by improving preventive actions and curative actions based on peer knowledge of the microbial communities causing cross-contamination to MPV along the process chain. Goal is to maintain safety and the high quality of food, while taking into account the environmental impacts of new techniques.

Aim of the project
SUSCLEAN is focused on minimally-processed vegetables (MPV). The project will contribute to the development and implementation of a new generation of environment-friendly equipment, sanitation and food product decontamination technologies ensuring food safety. The primary role of the RIVM, as leader of workpackage 1, is to evaluate newly developed decontamination techniques in terms of assuring microbial food safety. In addition, more knowledge is gained with respect to the ecology of pathogens associated with fresh vegetables.

The main focus of this work package is to study the biodiversity and dynamics of the native microbial communities as well as the colonisation patterns of pathogens.

- The biodiversity and the dynamics of the natural microbial ecosystem on MPV and equipment will be established along the production process. The physiological profile, mechanisms of biofilm development, genetic composition of the contamination (including antibiotic resistance), survival/(re)growth potential and virulence of salad and cantaloupe (freshly cut) associated spoilage bacteria and pathogens will be characterised.
- The effects of commonly used sanitising procedures will be studied on microbial survival and colonisation parameters cited above. A special focus will be performed on the role of biofilm formation in regard to the decontamination efficiency towards spoilage and pathogenic organisms on equipment.
- The impact of alternative decontamination methods identified in other workpackages of the SUSCLEAN project on the factors described above will be studied and compared to identify the most effective decontamination methods. In this case, the most effective ones are regarded as the combination between minimal persistence, minimal re-growth potential and minimal increased stress-resistance / pathogenic potential. In addition,

rapid-sensitive diagnostic tools will be developed in order to meet the needs for contamination survey along the supply chain.

Strategic and innovative aspects
SUSCLEAN will contribute to the development and implementation of a new generation of environment-friendly equipment sanitation and food product decontamination technologies ensuring food safety. This will lead to reduction of the use of water and chemicals (chlorine) up to 20-50%, whilst ensuring food safety, sustainable practices and preserving fresh-cut food European quality and competitiveness. A well-balanced partnership has been built with research institutes and industries (SMEs and one end-user large corporation). Moreover, the project is an excellent opportunity to strengthen EU networks and enhance the visibility of RIVM/CIb internationally.

Planned activities
- Year 1: Start with experiments on colonisation patterns, biofilm formation and characterisation of spoilage and pathogen microorganisms in the supply chain.
- Year 2:
  - Continuation of experiments on colonisation patterns, biofilm formation and characterisation of spoilage and pathogen microorganisms in the supply chain.
  - Start impact of innovative disinfection methods on pathogenic potential of bacterial pathogens and enteric viruses.
- Year 3: Continuation impact of innovative disinfection methods on pathogenic potential of bacterial pathogens and enteric viruses.

Planned products
Several peer reviewed publications.
Upgraded best available techniques documents.

Foreseen follow-up
SUSCLEAN will propose recommendations of emerging techniques to upgrade the IPPC (European Commission), in terms of reducing chlorine emissions in water and decreasing water consumption rates in food industries by up to 50 % via a revision of the relevant best available techniques reference document(s). The transfer of the developed knowledge to the European MPV industry in general, and SMEs in particular.

7 New dimensions in integrated (risk) assessments in public health and environment (IRA)

7.1 Strategic aims

Societal impact
A person's health and safety are affected by all sorts of outside influences including chemical compounds, radiation, food, and pharmaceutical products. Ecosystems are affected by many factors as well. Ultimately, the net impact of all such influences is determined by their combined effect.
This leads to growing awareness of the necessity of an integrated health policy to effectively deal with combined risk factors. New technologies may benefit society in one way but may become threats in another. The advantages and disadvantages of applied agents and (un)intended exposure have to be subject to constant consideration and evaluation. On the same note, threats can also arise from the harmful intentions of individuals.

Increasing knowledge about all sorts of risks is leading to many new policies and regulations designed to keep all of them at acceptable levels. Directives and regulations at European level are gaining importance at national and local levels, including obligations for the Netherlands.

Description and impact in relation to RIVM tasks
Whereas integrated risk assessments are not a novelty, the development of an advanced integrated set of instruments is still in its infancy phase. Risks are often determined by the combination of many different factors. Knowledge about relevant exposure and exposure-effect relations are crucial elements of risk estimation. Integration of this knowledge into relevant source-risk chains is vital (indispensable) for risk assessment.

RIVM has a long tradition of integrating knowledge, especially in the area of risk. In coming years, the institute will build on that tradition, if only because new risks continue to appear, risk management is becoming more complex and demand for integrated credible expertise is increasing. Growing directory responsibilities of RIVM in this field will eventually lead to a shift of activity emphasis toward knowledge integration. Integrated knowledge is also needed for the performance of statutory tasks, such as the assessment of health and environmental effects of chemical substances and radiation.
With the introduction of new advanced technologies, the prompt evaluation of potential negative effects on health and environment is essential. Risk integration is also relevant to assessments of other health-related issues such as informed consent, health hypes, and so forth. In many cases, no simple causal relationships exist but many factors affect public health or the environment in indirect and complex ways.

Governments, asked to set policies, want to know how society will likely progress. Integration of risk/benefit assessments and knowledge about societal change have been crucial to RIVM products such as the Public Health Status and Forecasting Reports (VTV) and the Dutch Health Care Performance Report (Zorgbalans). The integration of knowledge about societal development is indispensable to these products.

Focus and future direction of projects
This research theme aims to bring knowledge integration at RIVM to an even higher level. This requires the connection of the knowledge that will be generated in the other research themes as well as the knowledge that has been developed during the past years. It will include the development of new

instruments, such as improved or new models. Current models could be enhanced by adding new elements such as predicted effects of behavioural changes or consequences of skewed risk perception.
Other important elements that could be integrated in the new models include the economical perspective (cost-efficiency, socioeconomical analysis), the scientific policy perspective and risk governance (meeting norms, policy deficits, meeting policy targets).

The research theme will also enable studies of isolated risks, as they form the basis for future risk integration. Where appropriate, benefits should be studies as well as risks. Therefore, projects within this research theme could encompass any type of risk.

International connections
At present, integrated risk assessment is most actively pursued in the areas of (consumer) safety and the environment. The European Environment Agency lists 'integrated environmental assessment' as one of four goals. The World Health Organization and the European Commission's Directorate-General for Health and Consumers (DG SANCO) often stress the importance of looking at health threats in an integrated way. Both organizations put great value on 'health security', a term that aims to encompass all the various threats to human health.
The EU's 7th Framework Programme (FP7) provides options to submit proposals through the 'environment and health' and 'natural hazards' actions. Its 2010 Work Programme contains a call named 'new methodologies for multi-hazard and multi-risk assessment'.
The EU's 'Second programme of Community action in the field of health (2008 to 2013)' lists 'health security' as an area in which calls will be published.

Keywords
modelling, cost/benefit, Public Health Status and Forecasting Reports (VTV) food, microbiology, pharmaceuticals, chemical substances, ionised and non-ionised radiation, safety, new threats, key factors, health technology assessment, emerging technologies, advanced therapeutics, quantitative risk assessment, food additives, external safety, radiation, spatial planning, instruments for environmental effect assessment, cost-efficiency analysis

7.2 List IRA

Number	Title	Project leader	Int.
S/260256	Impacts of active transport in urban environments (AVENUE)	Wanda Wendel-Vos	
S/260266	Health equity impact	Mariël Droomers	
S/260276	Risk stratification in screening	Annemieke Spijkerman	
S/270226	Dutch DALYs 2.0	Coen van Gool	
S/270236	Towards an eco-epidemiology?	Johan Melse	
S/320003	Towards integration of quantitative toxicogenomics in human toxicological risk assessment (DR-omics)	Wim Mennes	
S/330146	Integration of quantitative microbiological risk assessment and epidemiology (QMRA)	Eric Evers	
S/340008	Assuring safety without animal testing (ASAT) for respiratory sensitization	Henk van Loveren	
S/601002	Synthetic Biology, Risk benefit evaluations in R&D and product application	Rik Bleijs	
S/607023	Integrated risk assessment nanomaterials (IRAN)	Willie Peijnenburg	
S/607024	Exploration of the nature, extent and policy relevance of potential ecological effects of radio frequency electromagnetic fields (PEER)	Willie Peijnenburg	
S/610004	SCARIER?	Harmen Bijwaard	
S/610020	D-Light&Food	Harry Slaper	
S/610020	D-light and food pre	Harry Slaper	
S/610021	Irradiance	Harmen Bijwaard	
E/630017	ENPRA	Ilse Gosens	*
S/630021	Oxidative potential exposure and risk assessment (OPERA)	Nicole Janssen	
S/630022	Healthy action	Hanneke Kruize	
S/630023	Investigating the role of individual attitudes in deciding about uncertain risks: a methodology (IRIDIUM)	Anne Knol	
S/630024	Characterization of idiopathic environmental intolerances (Chi2)	Irene van Kamp	
S/660021	Knowledge integration by physiologically based pharmacokinetic (PBPK) modelling	Claudine Hunault	

Int. = international project cofinanced by SOR-budget

7.3 Summaries

Title:	**Impacts of active transport in urban environments (AVENUE)**
Project number:	**S/260256**
Project leader:	Dr. ing. G.C.W. Wendel-Vos (Wanda) (V&Z-PZO)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 493,000

Motivation
Because of the increasing awareness of the environment and negative health effects of transport, the urgency for interventions and policies to reduce these effects and related risks is high. Active transport (walking and bicycling) has often been advocated as a way to improve individual health as well as a way to reduce air pollution, carbon emissions, congestion, noise, traffic dangers and other harmful impacts of motorized transport. To describe and compare the health impacts of active transport and to perform cost-effectiveness analyses of options for policies, the characterization and quantification of health impacts is required. To properly estimate health effects related to active transport, it is important to integrate methods and knowledge from several professions such as transport safety, urban planning, environmental health (e.g. air pollution, noise) and public health.

Despite a growing number of studies underlining the potential health benefits of a shift from motorized transport towards active transport, the number of studies using an integrated approach remains scarce. In previous studies, insight was obtained in the availability and quality of data, models and tools that are necessary to estimate the health benefits of these transport scenarios. For our assessment we were forced to make several assumptions with regard to exposure indicators, age groups, models, etc. The present study will elucidate these uncertainties by several in-depth investigations. In this process, expertise from different fields will be used in order to come to integrated solutions. The results of this project will enable more valid estimates of the expected long-term health effects of transport-related interventions, especially the effects of interventions that promote a shift from short car trips to short trips by active transport.

Aim of the project
The overall aim of the present study is to develop a method that is able to integrate health effects from various exposures related to policy measures promoting active transport. For this purpose, AVENUE aims to provide in-depth information on characteristics of short car and active transport trips, feasibility of replacing short car trips with short trips by active transport and the potential health effects of combined exposures during active transport.

Strategic and innovative aspects
The present study has a high strategic value both in international and scientific perspective. In the Netherlands, the proportion of active transport is exceptionally high compared to most other countries. Insight into factors that may positively influence active transport and into the health impact of active transport gives important information to policymakers and scientists around the world.

Innovative aspects of AVENUE are the multidisciplinary approach, the fact that conclusions will be based on a combination of qualitative and quantitative methods and the fact that mobility research will be used to link active transport to environmental factors and health. In contrast to other studies that study local situations, AVENUE will have a main focus on nationally representative data.

Planned activities

- Secondary data analyses on several existing datasets of the Mobility research Netherlands (in Dutch: Mobiliteitsonderzoek Nederland, MON). These analyses will provide insight into who is making short car, walking and/or bicycling trips, where these trips take place and for what reason.
- Additional data collection within MON in collaboration with Statistics Netherlands (CBS). This will, additional to existing MON databases, provide information on perceived health, regular physical activity levels, motives to choose particular routes and geographical details of the routes taken in relation to short car, walking and/or bicycling trips.
- Stakeholder analysis to identify potentially involved stakeholders for interventions/policy measures promoting active transport as opposed to motorized transport.
- Research among stakeholders: Existing intervention strategies to stimulate short trips to be made by active transport and their (long-term) effectiveness.
- Expert interviews: How (i.e. which mathematical/statistical method(s) should be considered and which are already in use) to develop a method/tool that incorporates the health effect of combined exposure during active transport.
- Data analyses additional MON data.
- Focus group interviews with individuals and identified stakeholders to gain insight into the proportion of the population who would be willing to change their mode of transport for short-distance trips (Reach), which potential stakeholders would be willing to participate in and/or to adhere to an intervention programme substituting short car trips with short trips by active transport, and to what extent proposed interventions could become a structurally part of routine organizational practices and policies.
- Continuing data analyses additional MON data.

Planned products

- Integrated method to evaluate the effectiveness of policy measures promoting active transport.
- PhD thesis.
- Six peer reviewed publications. Publications will comprise characteristics of short car and active transport trips, feasibility of replacing short car trips with short trips by active transport and the potential health effects of combined exposures during active transport.

Foreseen follow-up

The results of this project will enable more valid estimates of the expected long-term health effects of transport-related interventions, especially the effects of interventions that promote a shift from short car trips to short trips by active transport. Consequently, the results of this project will help governmental choices with regard to the approach for environmental factors in relation to environment and health. Results will be valuable to for example the Ministry of Health, Welfare and Sport, the Ministry of Infrastructure and the Environment

Title:	**Health equity impact**
Project number:	**S/260266**
Project leader:	Dr. P.C.A. Droomers (Mariël) (V&Z-PZO)
Start:	01-01-2011
End:	31-12-2013
Total SOR-budget:	€ 167,700

Motivation

All European countries are faced with substantial health inequalities within their populations. People with a lower level of education, a lower occupational class, or a lower level of income tend to die at a younger age, and to have a higher prevalence of most types of health problems. Differences in life expectancy at birth and at higher ages between the lowest and the highest socioeconomic groups, range from four to ten years for men and from two to seven years for women. Furthermore, socioeconomic health differences start at a young age and persist and widen in older ages.

Socioeconomic health inequalities also persist in the Netherlands. Very recently, the 2010 national health report confirmed the existence of socioeconomic gradients in health determinants, health status, illness and mortality. Negative health determinants and health risks accumulate within groups that are also socially disadvantaged in other respects. In addition, population groups with lower than average health status and healthy life expectancy are also most strongly affected by hurdles that may impact negatively on health service access. The WHO Commission on the Social Determinants of Health (CSDH) identified that fundamental changes in policy and practice would be required to address the underlying causes of health inequalities. One of the recommendations was the development of Health Impact Assessment (HIA) methods and tools with a specific focus on health inequalities. Even though existing HIA sheds light on differential impacts, the equity focus is often not rigorously addressed.

Aim of the project

This project will provide scientifically sound methods and tools to assess impacts of intersectoral policies on health inequalities, which are as yet not developed. Institutes across Europe using these tools will be better able to assist governments with best available evidence regarding these policy impacts. The tools developed will be of key importance for Health inequality in all policies approaches. Specific objective is to develop tools that can support a Health Inequalities in All Policies approach, by developing and assessing a methodology for Health impact assessment with an equity focus (HIAef), as well as for Health equity audits (HEAs), based on learning from practice. Much attention will be paid to the practical use of such tools. The methodologies will be tested on national level in the Netherlands and several other countries, on regional level in several other countries, as well as on European (EU) policy level.

Strategic and innovative aspects

HIA with an equity focus (HIAef) does not yet exist. The demand for HIAef methods and tools will increase in coming years, given the wide recognition of the key role of broad intersectoral cooperation (i.e. Health in All Policies approach) in reducing health inequalities

Advancing the methodological development of HIAef and HEA is expected to reinforce RIVM's position in the Netherlands as a national public health institute

that provides the best available evidence to Ministries and other governmental bodies. It will also strengthen RIVM's position as the lead institute on HIA and environmental HIA in the Netherlands.
The Netherlands has a strong international reputation in the field of impact assessment in general. More specifically, the international HIA community praises the Netherlands for its national level HIA expertise, while in most other countries the focus is more on local or regional (project) level HIA. The project will reinforce and enhance the position of RIVM and the Netherlands in this international environment.

Planned activities

- Discussion and agreement on a framework for Health Equity in All Policies at national level, and consider what its implications are for policymaking and coordination.
- Develop a common methodology and principles for HIAef and HEA together with other European partners.
- Review of relevant literature and contribute to European report on the current situation on the use made of HEAs and HIAefs in developing policy in participating countries,
- Carry out a full HEA in the Netherlands, simultaneously with trials by other partners in their respective countries, and refine methodology and principles based on the common experiences.
- Participate in at least one country-to-country exchange to share experiences and promote learning on processes used to include health equity in policymaking across government, including written report on learning experiences.
- Participate in international meetings and a health inequalities impact assessment conference.
- Contribute to a report on recommendations and findings for developing an equity focus across policies at EU, national and regional level.

Planned products

Two different output categories can be distinguished here:
Deliverables as a result of the international collaborative effort to which the RIVM team will contribute:

- A document describing the common understanding of project partners of a 'Health Inequalities in All Policies approach' to addressing inequalities, and its implications for policy and policy coordination at EU, national and sub-national levels.
- Report on the current situation regarding policy HIAs with an equity focus and Health Equity Audits in European member states.
- Publication of project learning, including tools and methodologies for HIAef and HEA, on the inclusion of health equity considerations into policymaking.
- Joint scientific article in a peer reviewed journal.

Specific products of the RIVM team, that will be delivered as results of the proposed SOR project:

- Scientific article for publication in peer reviewed international journal on the results of a Health Equity Audit of a national policy intervention in the Netherlands.
- Written summary of country-to-country learning and exchange event.

Foreseen follow-up

This project will provide methods and tools to assess impacts of policies on health inequalities, which are as yet not developed.

Institutes across Europe using these tools will be better able to assist governments with best available evidence regarding these impacts. The tools developed will be of key importance for Health in All Policies approaches.
The project results will be of importance for the EU processes regarding health inequalities stemming from the report of the Commission on the Social Determinants of Health, and to EU processes implementing the Lisbon Agenda where social exclusion is concerned.
In the Netherlands, better support can be given to ministries that wish to reduce health inequalities through healthy public policies.
The methodologies developed will be useful for the local/regional level in the framework of the Public Health Act, which requires municipalities to consider health impacts of their policies. The methodologies may be disseminated through the RIVM Centre for Healthy Living.

Title:	**Risk stratification in screening**
Project number:	**S/260276**
Project leader:	Dr. A.M.W. Spijkerman (Annemieke) (V&Z-PZO)
Start:	01-01-2011
End:	31-12-2011
Total SOR-budget:	€ 99,500

Motivation
Breast cancer is the most common cancer among women in the Netherlands. In 2007, 12,843 new cases of breast cancer were detected and a total of 3,180 women died of breast cancer. In 1989, a national screening programme for breast cancer among women aged 50-69 years was implemented. The extension of the screening programme to include women between 70-75 years of age was completed in 2001. All eligible women are invited for mammography every two years. In 2007, over 1.1 million women were invited for the screening and more than 900,000 screening mammograms were made. Of these, 16,000 were referred to the hospital for further evaluation and a total of 5,000 women were diagnosed with breast cancer. Thus, nearly 11,000 women received a false positive screening result. In addition, the number of false negative screening results is estimated to be 1,000 cases.
Risk stratification has the potential to improve breast cancer screening effectiveness and to reduce the number of false positive and false negative mammography results. Risk stratification allows screening to be tailored to the individual woman rather than to use one common approach for the entire screening population. For example, a woman with a high risk for breast cancer will be invited for screening every year, while a woman with a low risk might be invited every (two to) three years. This personalized screening approach might also improve the (cost-)effectiveness of breast cancer screening.

Internationally, there is a clear expansion of efforts to develop prediction models including lifestyle factors (such as alcohol consumption) and blood biomarkers in order to improve breast cancer risk prediction. However, an overview is lacking of the most recently developed risk stratification tools and their test characteristics.

Aim of the project
The general aims of this project are:
- To obtain state of the art knowledge on (the effectiveness of) risk stratification in breast cancer screening and disseminate/integrate this knowledge among breast cancer and screening researchers and stakeholders within RIVM.
- To explore and assess the quality of state of the art international breast cancer risk stratification tools.

Specific objectives are:
- Obtain up to date knowledge at RIVM on national and international progress in the field of risk stratification, aimed at a possible future application in the Dutch breast cancer screening programme. Both advantages and disadvantages of risk stratification will be studied.
- Address the research questions: what is the state of the art in breast cancer risk stratification and which tools have the best test characteristics?

Strategic and innovative aspects
Risk stratification in cancer screening has recently gained much interest from both researchers as well as stakeholders. For RIVM it is of vital importance to be informed of ongoing research efforts and results regarding risk stratification in cancer screening, to anticipate future developments in screening programmes. This project aims to do so by the formation of a multidisciplinary knowledge platform focused on the early identification of important developments in the new and innovative field of risk stratification in cancer screening. In this platform, five departments will collaborate and expand existing expertise on epidemiology, secondary prevention and molecular cancer research to risk stratification. Although the present proposal focuses on breast cancer screening, the knowledge obtained on the principles of risk stratification will also be applicable to screening of other diseases, for example colorectal cancer screening.

Planned activities
Obtain up to date knowledge at RIVM on national and international progress in the field of risk stratification, aimed at a possible future application in breast cancer screening:
- Study if and how risk stratification is applied in the screening setting in EU countries with a breast cancer screening programme.
- Investigate how risk stratification for breast cancer is used in clinical practice in the USA.
- Presentation of the results of this part of the project at the end of 2011 to the 'Programma Commissie Borstkanker screening' and to the relevant stakeholders of the Ministry of Health, Welfare and Sport (VWS).

To explore and assess the quality of state of the art international breast cancer risk stratification tools:
- Update of the systematic review of Cummings with breast cancer risk stratification models which have been developed from 2008 to 2010.

Planned products
- Multidisciplinary knowledge platform at the RIVM on risk stratification in breast cancer screening. This risk stratification knowledge is easily applicable to the screening and early detection of other diseases.
- Early alerts of new scientific developments to RIVM's Centre for population screening (CVB) and screening programme committees.
- Peer reviewed scientific publication on breast cancer risk stratification tools.

Foreseen follow-up
This project is essential for the further improvement of the screening programme for breast cancer in the Netherlands, it has the potential to limit harm and maximize benefit of the existing screening programme. It has high public health relevance as its results may affect the close to a million women who attend for breast cancer screening every year. Risk stratification before mammography may help to limit the number of false positive and false negative mammography results in the future. It may also be used to tailor the screening interval to the individual woman: screen every year in high risk women, but once every three years in low risk women.
RIVM will benefit because this project facilitates anticipation of future developments in screening programmes. Individually tailored screening through risk stratification is envisioned to be the screening strategy of the future. This project will provide the relevant state of the art knowledge and expertise.
The Ministry of Health, Welfare and Sport will be able to use the knowledge obtained in this project for their policy about breast cancer screening in the Netherlands. This project facilitates future assignments of the ministry to RIVM.

Title:	**Dutch DALYs 2.0**
Project number:	**S/270226**
Project leader:	Dr. C.H. van Gool (Coen) (V&Z-VTV)
Start:	01-07-2011
End:	31-06-2013
Total SOR-budget:	€ 465,300

Motivation
Worldwide the Disability Adjusted Life Year (DALY) is a well-accepted measure to use in prioritizing public health issues. The DALY combines the population health indicators mortality, morbidity and disability into one measure. Its main use lies in quantifying the burden of disease (BoD) and comparing the health status of different populations.
For every disease, the DALY can be calculated as the sum of years lost due to premature death (years of life lost) and years lived in less than full health (years lived with disability). The latter amount is calculated as: prevalence * disability weight. The disability weight, which specifies the severity of the disease, is thus a crucial element in BoD calculations. Following WHO's (World Health Organization) 1990 Global BoD study (1996), the four-yearly RIVM Public Health Forecasting Reports have been reporting on the BoD in the Netherlands, including top 10 lists of diseases with the largest impact on population health, from 1997 onward. The disability weights that were derived for the first Dutch BoD study in 1997 have frequently been used in international research

Current Dutch BoD studies fail to address the concept of comorbidity in BoD estimates. Generally, comorbid diseases jointly have less impact on a person's health than would be expected based on the separate diseases. Ignoring comorbidity therefore leads to inaccuracies in BoD estimations, since ageing populations include large proportions of persons with two or more diseases. Recent Dutch estimates mention 1.3 million persons having two or more diseases.
In order to study the impact of comorbidity on Dutch BoD estimates, recent data on the prevalence of diseases and comorbidity, as well as accurate disability weights are needed. The weights currently used are almost 15 years old, and in

this period health care has improved and many diseases now have lesser complications and therefore lesser impact on population health.

In 2007, the University of Washington, WHO, and the University of Queensland, in collaboration with Harvard University, and the Johns Hopkins University, initiated the new Global Burden of Disease Study 2005 (the GBD 2005 Study). Its major aim is revising the 1990 Global BoD studies by systematically comparing and qualitatively assessing availability of data and calculation methods, in order to be able to make 2005 DALY estimations comparable to 1990. The GBD 2005 Study is renewing the range of disability weights, but will attempt to adjust for comorbidity in BoD estimates.

Aim of the project

The goal of the proposed project is to validate and apply the GBD 2005 Study revised disability weights to the Dutch situation, and to use these validated disability weights for developing disability weights that take comorbidity into account, and to implement the burden of comorbidity on population health in a new Dutch BoD study. The total BoD in the Dutch population based on newly developed disability weights for comorbidity will be compared to estimates based on adjustment for comorbidity (as done in the GBD 2005 Study) to evaluate the added value of developing comorbidity disability weights.
Validating the revised disability weights entails that we have to make sure that the epidemiological information available in the Netherlands matches the international definitions of the diseases covered by the GBD 2005 Study disability weights. In case of a mismatch we will have to derive new disability weights, specific to the Dutch situation.
Disability weights taking comorbidity into account will be developed based on either additive (summing separate disability weights), multiplicative (multiplying separate disability weights) or maximal limit (using the highest disability weight of the separate conditions) methods in combination with valuating methods using panel studies.

Strategic and innovative aspects

Showing commitment to address the intricate issue of comorbidity in BoD research could strengthen RIVM's ties with BoD research entities, offer prospects for future invitations to cooperate in research, and position RIVM into a significant role in the international field of BoD research. Furthermore, successful completion of the project enhances public health monitoring in the Netherlands, one of RIVM's statutory tasks.
This project's primary innovative character compared to former (Dutch) BoD studies is best reflected in our unprecedented objective to develop disability weights that take comorbidity into account, using validated disability weights and state of the art modelling approaches. These comorbidity disability weights can then be used to implement the burden of comorbidity on population health in a new Dutch BoD study.

Planned activities

Validation/application GBD 2005 study disability weights:

- Retrieve revised GBD 2005 Study disability weights, as well as the methods and epidemiologic assumptions used to derive them.
- Retrieve epidemiologic information on (co)morbidity and mortality in the Netherlands from general practice registries, Statistics Netherlands, NIVEL, Trimbos institute, and other sources.

- Determining extent of accordance between abovementioned steps; if necessary start deriving alternative matching disability weights to Dutch situation.

Comorbidity disability weights development:
- Apply for Dutch EQ5D and/or SF-36 data at NIVEL, Trimbos institute, and CBS; possible other sources: Maastricht University, RIVM (Doetinchem Cohort).
- Performing preliminary analyses to determine most prevalent combinations of conditions.
- Organizing expert meetings to determine choice for comorbid conditions, determine analysis or modelling strategy per combination of comorbid conditions.
- Development of comorbidity disability weights through simulation models and panel studies.

Implementing comorbidity disability weights in Dutch BoD study:
- Applying the revised set of GBD 2005 Study and self-developed disability weights to the Dutch situation (input for Dutch BoD study).
- Using simulation modelling to determine the extent of comorbidity in the Netherlands.
- Applying the comorbidity disability weights to the Dutch situation.
- Preparing the results of the Dutch BoD study for publication in the 2014 Public Health Forecasting Report.

Planned products
- Disability weights that can be applied to the Dutch situation.
- Calculations on the extent of BoD over- of underestimation.
- Approximately five peer reviewed publications.
- Contribution to 2014 Public Health Forecasting Report.

Foreseen follow-up
Project outcomes will be used as input for the Dutch National Public Health Compass and the Dutch Public Health Forecasting Report 2014, as commissioned by the Ministry of Health, Welfare and Sport (VWS). These latter products are highly appreciated tools for policymakers that assist them in formulating future assignments in various fields. Outcomes can assist policymakers in establishing priorities in health care and health interventions and in comparing the health status in the Netherlands to that of other countries.
As several RIVM departments and (inter)national research institutes have frequently used (elements of) our Dutch BoD calculations, it is anticipated that our comorbidity disability weights as well as other elements of the revised BoD calculations again find practical use in products of other RIVM departments, as well as of organizations outside RIVM and outside the Netherlands.

Title:	**Towards an eco-epidemiology?**
Project number:	**S/270236**
Project leader:	Ir. J.M. Melse (Johan) (V&Z-VTV)
Start:	01-01-2011
End:	31-12-2012
Total SOR-budget:	€ 200,000

Motivation

Epidemiology is one of the foundations of public health. Thus, it is also one of the pillars under much of the public and environmental health work at RIVM - National Institute for Public Health and the Environment in the Netherlands. After the sanitary statistics more than 100 years ago, the focus of epidemiology focus moved to infectious diseases, and from the fifties on to chronic diseases. This has resulted in a multitude of scientific insights and angles of actions for health prevention and policy.

However, it is not immediately clear whether we should continue on this track. The easy-to-reach 'risk fruit' seems to be harvested by now or at least the evidence base for the main issues has been well established. New risks for health are still being discovered but are often very small. More importantly, their impacts on public health are seldom evident, resulting in epidemiological confusion amongst both public and prevention professionals and reducing trust in science and government. Also, inequalities in health persist over the years, partly because health promotion through behavioural changes proves to be more difficult than hoped for. In addition, in this genomics era awareness is growing that people are (genetically) more different to each other than anticipated before. This results in different health outcomes in response to (environmental) interactions, instead of a 'one size fits all' approach. It is questionable whether the present approach to chronic disease which emphasizes risk factors at the individual level, is still adequate to deal with the complex health challenges of today and of the future. It is estimated that the current chronic disease approach explains only a third of the causes of illness.

In short, there is need for new approaches, new paradigms for epidemiology and public health of the 21st century. Existing and established approaches necessarily need to be complemented, challenged and questioned by emerging ones. One of the more promising candidates is a so called 'ecological' or eco-epidemiology, largely based on system theory (which generally refers more to a way of thinking and doing science, more than to a well defined theory). In such a more ecological approach human beings are defined as systems, which consist of other systems while at the same time being part of larger ones.

Aim of the project

The aim of this project is to explore alternative or additional approaches and paradigms in epidemiology and public health, with focus on ecological, systems and complexity theory epidemiology.

Specific objectives are:

- To characterize current approaches in epidemiology and public health, their strong and weaker points and the boundaries these are facing in the light of contemporary and future public health challenges.
- To study alternative approaches and come up with a first articulation of a new paradigm from a more ecological or systems theory viewpoint.
- To explore the implications of such a new paradigm for data, research, concepts, models, policy and action in public health.
- To apply the new approach to a concrete example of a complex and policy relevant problem, in order to study its feasibility and practical potential.

Strategic and innovative aspects

Current epidemiology has been characterized as 'prisoner of the proximate'. This SOR-project is innovative in attempting to break at least some of the bars: from genes to individuals to (sub)populations, determinants of health and disease at all levels, and taking account of critical moment in the (distribution of) chances on health in time and space.

Going beyond the current risk factor approach to a broader view leads to better understanding of the complex nature of the web of causal pathways to health and disease through all levels, together with differences in pathways and resilience between various (sub)populations. The project thus has potentially far reaching impacts on how we think about disease and health, as well as how we model, study and act upon public health issues.

Since the 1990s, a number of calls for such a paradigmatic shift have been heard, however with apparently few tangible results, especially for the non-communicable diseases. This project not only aims to go beyond current practice and thinking, it will explicitly do so in a concrete way focusing on practical applicability. As such it is of strategic importance in furthering RIVM's position as a leading institute in public health.

Planned activities

- Literature review resulting in a first formulation of a new approach.
- Applying the new approach to concrete and complex example.
- National en international expert meetings.

Planned products

- Presentations at international conferences.
- Peer reviewed (international) journal articles.
- An RIVM internal report, with clear conclusions on feasibility and directions for further research, together with implications and recommendations for RIVM models and research. Depending on the results, a subsequent project will be outlined.
- Products for dissemination for broader public: web article for RIVM-website, professional publication.
- Building and contributing to (inter-)national networks.

Foreseen follow-up

The results of this exploratory project will be profitable to many, in the first place for RIVM itself. A new approach or paradigm in epidemiology and public health can produce new insights and open up new avenues in conceptual understanding of and research in public health. Depending on the results of this exploration, a more extensive project will lead to improving the currently used conceptual and quantitative models of public health available at RIVM. These will be utilized for the next Public Health Status and Forecast and other products in public health and environment.

Further, the exploration in this SOR-project may contribute to streamlining within RIVM the way we think, act and communicate on risk and epidemiology. This will reduce inconsistent messages tot public and policy, promoting trust in RIVM.

Secondly, through improved understanding of the way health and disease are produced and distributed within populations and embody social structures based on the exploration of a new paradigm, RIVM can eventually help policy and prevention to devise different and more effective ways to improve the public health and reduce inequalities.

Title:	**Towards integration of quantitative toxicogenomics in human toxicological risk assessment (DR-omics)**
Project number:	**S/320003**
Project leader:	Dr. W.C. Mennes (Wim) (VGC-SIR)
Start:	01-01-2011
End:	31-12-2012
Total SOR budget:	€ 120,000

Motivation

Over the last decade genomics, proteomics and metabolomics technologies have influenced the field of toxicology enormously. Toxicogenomics is the application of genomics-based technologies in toxicology. In various legal frameworks for (industrial) chemicals, but particularly in REACH (Regulation, Evaluation, Authorisation and Restriction of Chemical substances), the use of toxicogenomics in risk assessment is anticipated. Toxicogenomics data can lead to the identification of the mode of action of chemicals or drugs. Furthermore, some scientists consider toxicogenomics as a major possibility to replace tests using experimental animals. Currently, toxicogenomics is predominantly used as a tool for the elucidation of a mode of action and thus for hazard identification of a chemical. In line with this, projects using toxicogenomics were mainly focused on hazard identification. In our previous SOR project Toxicogenomics in risk assessment (S/340010) it was demonstrated, as a proof-of-principle, that by using toxicogenomics in a category approach we were able to distinguish reprotoxic phthalates from non-reprotoxic phthalates based on differential gene expression profiles. Therefore it is anticipated that toxicogenomics can support category approaches, which may lead to a cost-effective way to prioritize toxicity testing, aiming at hazard assessment and classification of large numbers of chemicals in a relatively short period of time.
Despite all these efforts and all the information obtained, toxicogenomics is still not ready as a tool for human toxicological risk assessment. This is mainly due to the fact that, to our knowledge, only very few studies have focused on dose-response relationships at gene expression level. In order to integrate toxicogenomic endpoints in quantitative risk assessment it is essential to know if relevant changes in gene expression occur in a dose-dependent manner and how these changes should be interpreted, i.e. to know at which levels of exposure changes in gene expression represent adverse effects. The outcome of this project will contribute to the discussion on the implementation of toxicogenomics techniques in integrated testing strategies, which are being developed as tools to reduce animal testing.

Aim of the project

The aim of this project is to investigate if and how toxicogenomics can be used as a tool in quantitative risk assessment of human health. We will focus on both the scientific value and the possibilities and limitations of the use of toxicogenomics for hazard identification and quantitative risk assessment.
More specifically, we will discuss:

- The current state of the art of toxicogenomics in risk assessment based on our own data and literature reviews.
- What risk assessors expect from toxicogenomics in risk assessment.
- The limitations of toxicogenomics for risk assessment.
- How these limitations can be resolved, i.e. how a quantitative toxicogenomics experiments should be performed.

Strategic and innovative aspects
As indicated by the National Research Council in their report 'Toxicity testing in the 21st century', the time has come for more innovative approaches to toxicity testing. Since the project is unique in the sense that it deals with quantitative aspects of toxicogenomics whereas others remain at the hazard level. Consequently, the outcome of this project will strengthen RIVM's position in (inter)national activities already started by International Programme on Chemical Safety (IPCS), Organisation for Economic Cooperation and Development (OECD), United Stated environmental protection agency (US-EPA) and theNetherlands Toxicogenomics Centre (NTC).
It is anticipated that in near future toxicogenomics will be integrated in testing strategies, and as such will become a standard technique in toxicity testing. The strategic aim of this project is therefore to advance understanding of the possibilities and limitations of the use of toxicogenomics in toxicological risk assessment.

Planned activities
In this project we study if toxicogenomics can be used as tool in risk assessment:
- We will start in this project with a literature search to identify and evaluate current efforts to make toxicogenomics quantitative. The result of this work will provide us with a minimum set of criteria to which a toxicogenomics study should be compliant to allow for derivation of reliable dose-response information.
- Simultaneously, national and international experts in the field of toxicological risk assessment will be asked to give their ideas about minimum set of criteria requirements to derive reliable dose-response information from such studies.
- The information obtained from literature and the views expressed by the (inter)national experts will be assembled to give a definitive minimum set of criteria.
- Existing data sets, either from literature or data obtained in related RIVM projects will be evaluated against these criteria to investigate whether within these data sets adequate dose-response information can be identified
- Based on the results of this evaluation a proposal for a study protocol will be derived.

Planned products
- Up-to-date knowledge on (inter-)national progress in the application of toxicogenomics for risk assessment.
- The results will be submitted for publication in (an) international peer reviewed journal(s). If applicable, the results will also be published as an RIVM report.
- Publication(s)/report on feasibility of the use of quantitative aspects of toxicogenomics in toxicological risk assessment. This (these) communication(s) will not only describe current state-of-art, the view of (inter)national experts and the preliminary results obtained with our list of criteria, but more importantly, it will also contain a suggestion for a protocol for future quantitative toxicogenomics studies.
- Alternatively, this (these) communication(s) may provide an inventory of needs for further data and a follow-up study proposal.

Foreseen follow-up
The most important benefits of the projects are:
- Several RIVM laboratories will be able to judge the value of toxicogenomics data for human toxicological risk assessment.
  The outcome of this project may contribute to, ultimately, an improved, more mechanism-based risk analysis of chemicals.

- Furthermore, the knowledge obtained in this project will give RIVM an excellent position to contribute to international activities such as already initiated by IPCS, OECD and US-EPA, and the Netherlands toxicogenomics centre (NTC). In Europe, RIVM will be able to contribute to the development of integrated testing strategies needed in various regulatory frameworks such as REACH. Furthermore, this project will strengthen our position in future expert advice to regulatory entities.

Title:	**Integration of quantitative microbiological risk assessment and epidemiology (QMRA)**
Project number:	**S/330146**
Project leader:	Dr. E.G. Evers (Eric) (CIb-LZO)
Start:	01-07-2011
End:	01-07-2013
Total SOR-budget:	€ 310,200

Motivation

Two separate scientific disciplines aim to estimate the incidence of illness due to exposure to pathogenic microorganisms via food, water and the environment. These are epidemiology (using e.g. cohort studies, outbreak studies, subtyping studies, case control studies) and quantitative microbiological risk assessment (QMRA; using mathematical models of exposure and dose-response relationships, which have been derived from experimental studies). The two approaches have a different starting point: while the epidemiological approach starts from the total incidence of disease and calculates the attributable fraction, the QMRA approach starts out with exposure data and calculates the number of cases for each exposure route. There is (limited) interaction between these two disciplines as they study the same system, but there is currently no analytical framework to integrate results from these two disciplines.

The most important interfaces between these disciplines that can be distinguished are estimates of attribution, total number of human cases for a pathogen, and numbers of human cases for specific pathogen-transmission route combinations. The results from the different disciplines can be very different, which is unsatisfying from a scientific point of view, but it also poses problems for risk management: two very different estimates of the size of specific public health risks makes it difficult to choose intervention measures from a cost-effectiveness point of view. A second important aspect, which is relevant both for each discipline separately and for comparing the results between these disciplines, is the limited attention to uncertainty. Currently, the full range of uncertainty in calculation results of both disciplines is incompletely known and the reliability of these results is difficult to judge. Uncertainty can for example derive from variation in measurement, interpretation of the outcomes, or from differences in the chosen models, assumptions, or definitions. Some types of uncertainties can be quantified; others can only be assessed in qualitative terms. In current practices, scientific research often only acknowledges a small part of – mainly the quantifiable part of – uncertainty. It is expected that by using Bayesian methods, which are flexible in implementing different levels of stochasticity, the analysis of statistical uncertainty of the parameters and data in the models problem can be improved. More attention is needed for applying a good framework to handle this, but this is complicated by the fact that such frameworks are still in an early phase of development.

Aim of the project

The overall goal of this project is to provide a theoretical and practical basis for interaction and integration of methods and results in QMRA and epidemiology, taking into account parameter estimates and assumptions with corresponding uncertainties, into one framework which is expected to lead to less uncertain estimates of numbers of human cases and attribution, by a mechanism of mutual 'borrowing strength'.

The main objectives of this project are to:

- Explore, identify and characterize the uncertainty in each approach.
- Analyse the effect of sources of uncertainty on model output in both disciplines.
- Investigate the main causes and implications of the differences in the results between the approaches of the two disciplines.
- To provide an integrated framework for harmonized estimates and comprehensive uncertainty assessment of public health risk of pathogens that are commonly transmitted by food.
- Explore the implications of the project results for decision-making under uncertainty.

Strategic and innovative aspects

The innovative nature of this project involves the provision of a theoretical framework for combination and integration of two closely related disciplines (QMRA and epidemiology) that currently does not exist for assessing the public health risks of infectious diseases. Both disciplines will certainly benefit from the interaction between experts and the exchange of concepts, definitions and theories. More specifically, estimating numbers of cases and attribution, while integrating information from QMRA and epidemiology through sound theoretical frameworks has to our knowledge not been done before. The thorough analysis of uncertainty that necessarily precedes this integration is of importance in itself and has as yet rarely been done in the field of the public health risk of infectious diseases.

Planned activities

- Model retrieval and adaptation for current project. Develop a typology of uncertainty and assumptions that can be applied to the relevant QMRA and epidemiological models and characterize the different types of uncertainties in each approach as good and quantitative as possible.
- Analysis of the effect of a selected set of relevant sources of uncertainty on results obtained in both disciplines using e.g. Monte Carlo simulation, regression models, scenario analysis, construction of Bayesian Belief Networks, Numerical Unit Spread Assessment Pedigree, a system for multidimensional uncertainty assessment (NUSAP) and other methods as included in integrated environmental health impact assessment (IEHIA).
- Compare the results of QMRA and epidemiology, taking the new obtained information on uncertainty into account and identifying sources of uncertainty that may cause the differences in results between these disciplines.
- Development of a theoretical (and to the extent possible also a practical) framework to integrate QMRA and epidemiology estimates.
- Provide new estimates including uncertainty on the number of human cases and attribution using a Bayesian network, NUSAP and other methods that can be employed to deal with uncertainties in IEHIA.

Planned products

- Two peer reviewed publications.
- RIVM report, which gives a better opportunity to describe extensively the findings and results for future use.

- Presentations on congresses.
- The development of a network of risk assessors and epidemiologists that are prone to interdisciplinary cooperation.

Foreseen follow-up
Policymakers need to base their decisions on scientific evidence which takes proper account of factors that limit the quality of evidence which can be achieved with quantitative scientific methods.
Examples of this are underlying uncertainties and the inescapability to make assumptions that cannot (yet) be validated. The ability to deliver one coherent message on attribution and numbers of human cases of infectious disease, including a realistic estimate of uncertainty, will be much appreciated by the Ministry of Economic Affairs, Agriculture and Innovation (EL&I) and the Ministry of Health, Welfare and Sport (VWS) and European bodies such as the European Food Safety Authority (EFSA) and the European Centre for Disease Control (ECDC). This project will focus on *Campylobacter* in the food domain, but the methodology will be widely applicable for food and environmentally transmitted pathogens and we would expect further commissioned work in this direction.

Title:	**Assuring safety without animal testing (ASAT) for respiratory sensitization**
Project number:	**S/340008**
Project leader:	Prof. dr. H. van Loveren (Henk) (VGC-GBO)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 723,200

Motivation
The prevalence of asthma has been rising over the last decades. Chemical-induced respiratory allergy and resulting occupational asthma affects workers in many different occupations, for example in metal, rubber, pharmaceutical, cosmetic and chemical industry, in spray painters, and in hairdressers. It is estimated that approximately 9-15% of the adult asthma cases are acquired occupationally. The incidence of occupational asthma is estimated to be 200-300 new cases per million people per year, i.e. approximately 3000 – 4000 cases per year in the Netherlands. Common respiratory sensitizers are acid anhydrides, isocyanates, reactive dyes, and metal salts. It is as yet unknown what the incidence of respiratory sensitization is in consumers. Currently, chemicals are classified as a respiratory sensitizer based on human evidence, since there are no validated animal models. The mouse Local Lymph Node Assay (LLNA) is validated to identify all sensitizers, i.e. skin and respiratory sensitizers. Analysis of cytokine profiles in the context of this test informs on whether the tested compound is a skin or a respiratory sensitizer.
Under REACH (Registration, Evaluation, Authorisation and Restriction of Chemical substances), testing for sensitization is mandatory for chemicals produced from 1 ton per year. The preferential use of alternatives for animal testing is stipulated in the regulation. Respiratory sensitization is indicated as a priority for protection, but no testing strategy is proposed, indicating the knowledge gap. So far, proper risk assessment of respiratory sensitizers has been hampered by the lack of adequate exposure information, adequate animal or in vitro models for prediction of respiratory sensitizing activity, and data on the intrinsic potency of respiratory sensitizers. Setting limits for exposure to low

molecular weight compounds has proven to be very difficult and often not possible because of these deficiencies.

Aim of the project
The aim of the current research proposal is to develop an innovative animal-free strategy for prediction and risk assessment of respiratory sensitizers. Such a strategy may assist the design of a new framework for better human risk assessment without animal testing, and fits in the concept of ASAT (Assuring safety without snimal testing). The objectives to fulfil this aim are to design a framework for risk assessment based on the most adequate novel building blocks, at which dedicated experimental research should be targeted. In this framework (system) biology will assist the integration of available knowledge in humans and knowledge derived from studies previously carried out in animals.

Strategic and innovative aspects
Respiratory sensitization is indicated as a priority for protection. No valid assessment of the risk of chemical associated respiratory sensitization is currently in place. This project aims at designing such an approach, and for this reason it can be judged as innovative. In addition, the approach will not use laboratory animals, which will circumvent the uncertainty of animal to human extrapolation. The approach will take as starting point a crucial component of the adverse health outcome that needs to be protected, and that can be addressed experimentally. As this project will focus on the possibilities and limitations of implementation of a new framework for human risk assessment the contribution of regulators is essential in this project.

Planned activities
Planned activities are:
- Comprehensive literature search.
- Recruiting individuals exposed to and suffering from low molecular weight chemical sensitizers.
- Harvest of sputum and lung lavages and identify selected markers (cytokines and chemokines) in these materials that will be associated with the occupational disease of these individuals on the one hand, and also with their exposure on the other.
- Subsequently, for the purpose of this project test compounds with known respiratory will be selected. We will ensure that among these model chemicals there are chemicals to which exposure had occurred in the exposed individuals that we will study.
- With these chemicals we will follow an Integrated Testing Strategy that has been outlined in a workshop organized by the ASAT initiative; the required in vitro model is available at RIVM, but needs to be optimized for the project.
- Toxicogenomics analysis will be performed.
- All the data that are available from literature and from ongoing projects with a link to the current project, as well as information that will come available from the activities within this project itself will be put in a framework an integrated model that comprises all results, and in which dose-response relationships will play a prominent role, and which is aimed at evaluating the risk of sensitizing activity of exposure to chemicals. Coming to a single conclusion based on all different information blocks which are taken into account in the Integrated testing strategy ITS can be a non-transparent, subjective matter, especially when expert judgement is involved, and when different information sources are contradicting each other. The methodology developed within OSIRIS (European project) for the endpoint skin sensitization is expected to be readily applicable to the building blocks in the ITS for respiratory sensitization which are gathered in this proposed project.

- Based on the first phase of the project, the model and the read outs that it incorporates and that best describe the risk of the model, compounds will be selected for the purpose of performing a risk assessment of acid anhydrides.

Planned products
- A strategy for risk assessment of the respiratory sensitizing capacity of low molecular weight chemicals that will not use animal testing. The model will comprise an ITS based animal free approach.
- A risk assessment will be made, and health based setting recommended occupational exposure limits will be proposed for acid anhydrides, which has hitherto not been possible
- Publications in peer reviewed journals.
- PhD thesis.
- International Workshop.

Foreseen follow-up
The outcome of this project will be fueled into (inter)national bodies concerned with risk assessment of chemicals such as Dutch authority for food and consumer products (VWA), Dutch health council, the European Commission's Directorate-General for Health and Consumer Policy EU SANCO, Organisation for Economic Cooperation and Development (OECD) and International Programme on Chemical Safety (IPCS).

Title:	**Synthetic Biology, Risk benefit evaluations in R&D and product application**
Project number:	**S/601002**
Project leader:	Bleijs, dhr. dr. D.A. (Rik) (MEV/SEC)
Start:	01-01-2012
End:	31-12-2014
Total SOR-budget:	€ 345.200

Motivation
Synthetic Biology (SB) is defined as 'the design of biological systems that do not occur in nature', as well as 'the redesign of existing, natural biological systems'. SB integrates genetic engineering with comparative and functional genomics, bioinformatics and systems biology findings.
Successful examples of SB are the construction of synthetic viruses (e.g., poliovirus and influenzavirus), of a bacterial genome (Mycobacterium mycoides) and the production of compounds, such as the anti-malaria artemesinin in an industrial microorganism, based on the redesign of a complex metabolic pathway from a plant origin.

This project will focus on the risk assessment for three specific groups of 'living' SB products which are expected to have a substantial impact on society in the (near) future:
- Novel micro organisms designed to serve the bio-based economy through the biosynthetic production of bio-fuels, bio-plastics and chemicals, and biodegradation of organic pollutants.
- Modified viruses or bacteria producing and delivering novel pharmaceutical products in vivo for medical application in gene therapy.
- Live synthetic vaccines derived from redesigned and optimized viral genomes for use in humans and animals.

The development and subsequent introduction of such SB products will pose new questions in risk assessment and create the need for new assessment paradigms. New, successfully developed SB products will require marketing authorisation for which risk assessments concerning the environment, patient safety and public health will have to be made before these products can be approved. In case of a medical application of gene-therapeutics or live viral vaccines, current risk assessment methodologies and potential safety issues for patients are not well suited.
Not only new risks and uncertainties can be foreseen for this new technology; there is also an ambiguity challenge. SB can be characterized by high complexity, uncertainty and ambiguity. An effective, efficient and politically and legally feasible risk management strategy has to cope with these three challenges. Dealing with ambiguity necessarily leads to discursive management tools or communicative processes, taking social-analytical as well as normative viewpoints into account. Value conflicts have to be resolved; a fair treatment of concerns and visions will have to be assured.

Aim of the project
The aims of the project are to develop:
- New risk assessment methods applicable to the new products that will result from SB.
- A risk management strategy in which risks, uncertainties and ambiguity for SB are dealt with.

This project will do so by focusing on three specific groups of SB products: biofuels and biosensors, gene therapeutics and viral vaccines. Specific objectives, related to the three products groups, are:
- Literature review on state of the art developments in SB, focused on the three product groups mentioned.
- Identification of gaps in current risk assessment methods applied for the environment, and in safety issues for patients and public health.
- Inventory of risks, uncertainties and ambiguity.
- Development of new risk assessment methods and testing by expert panel.
- Gathering advise and expertise on how to cope with risks, uncertainties and ambiguity of a new technology, like SB in order to build on a consensus seeking discourse and to find suitable (communication) instruments (e.g stakeholder consultation).

Strategic and innovative aspects
RIVM is a key player in the risk assessment of genetically modified organisms, medicines and medical applications, chemicals and nanotechnology. By means of this project RIVM can position itself in the new field of SB by acquiring and sharing knowledge on the potential risks (and if possible benefits) of SB. This project enables RIVM to advise the government in finding the connection with existing legislation and in setting the policy agenda.
This project will give RIVM the head start needed to lead and participate in the debate on how to support and translate this new technology into national and EU regulatory requirements. It also will give RIVM a leading position in communicating risks and uncertainties of emerging technologies.

Planned activities
The project will be divided in several steps.
- The first step focuses on an inventory of SB risk analysis methodologies and identification of possible risk analysis shortcomings. During this phase an extensive study of the literature is planned as well as regularly discussions

with the expert panel and stakeholder consultation. On basis of the outcome risk assessment methods specific for SB will be developed.
- The next step a risk communication strategy for SB will be developed based on a study on risk benefit analysis and communication advice. The expert panel will also play a vital role during this phase of the project.
- In parallel with the step on risk communication three peer review articles will be produced on risk/benefit analysis and risk assessment for SB. The content of these publications is dependent on the results of the previous mentioned steps in the project.
- The final step is the presentation of the outcome of the project results in a report.

Planned products
Main foreseen products:
- Risk assessment methods applicable to SB products.
- Three peer reviewed publications on risk assessment methods and risk-benefit evaluation related to the three groups of SB products.
- RIVM report on new approaches for the risk assessment of SB products. Report presents advices for national and EU regulations.

Foreseen follow-up
For the environmental risk assessment methodology a widening of its scope from genetic modification to the products and technologies of SB will be created. A follow up project for developing guidance in risk-analysis can be foreseen and will be discussed with the Ministry of Infrastructure and Environment and possibly other departments.
Furthermore knowledge gained in this project is highly relevant for international organizations like OECD and EMA. In the EMA road map to 2015 they have indicated that with respect to Synthetic Biology there is a need for debate on how best to support and translate new science in regulatory requirements. The outcomes of this project will position RIVM and its Dutch experts in the centre of these discussions.

Title:	**Integrated risk assessment nanomaterials (IRAN)**
Project number:	**S/607023**
Project leader:	Prof. dr. ir. W.J.G.M. Peijnenburg (Willie) (MEV-LER)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 760,000

Motivation
Dosimetry is one of the pillars in the risk assessment of chemicals, usually expressed in mass (g) as a dose per mass body weight, soil or sediment (kg) or per volume of water or air (l or m^3). So far, the dose of mass was also used in the area of exposure to particulates. With the more recent development of particulates in the nano-range it became clear that mass as dose metric is not suitable to express responses induced by manufactured nanoparticles (MNs). The unique properties of these newly engineered nanomaterials have accelerated a large number of emerging technologies, resulting in many, often beneficiary, applications. Concern is, however, raised on possible adverse effects on man and the environment due to the release of especially free, insoluble and/or non-degradable MNs which in view of their potential persistence and accumulation have the highest priority for risk assessment. A main problem for IRA of MNs is how to express and quantify the effective dose. Problems associated to the lack of a suitable dose metric is that at present each

nanoparticles with slightly different characteristics, e.g. 20 nanometre (nm) versus 50 nm, spherical versus ellipses, coated versus non-coated, should in principle be assessed separately for environmental and human health risks. Various alternatives have been suggested to be added to or replace the mass metric, including number of particles, volume of the dose, and total surface area. In addition to size also other characteristics were suggested to use for the description of the nanoparticles like surface charge, specific surface area, surface reactivity, surface coating and composition, and shape and morphology. However, none of these characteristics nor combinations thereof have up till now been shown to be generally indicative for the dose metrics for IRA of particles. Due to the fact that the characteristics of the MNs at the site of action are expected to differ from the characteristics in the external exposure, it is the actual local dose at the site of toxicity for which a relationship between the dose metric and the toxic effect needs to be determined. Yet, up till now the external dose or total exposure concentration is used for risk assessment as this is the available parameter. This is independent whether the target site consists of human or environmental receptors. In addition, the most suitable dose metric for certain effects may be dependent of the mechanism of toxicity.

Aim of the project

The aim of the project is to understand, assess, and implement in risk assessment, the dose metric(s) that is (are) most suited for modelling the dose-effect relationship of MNs for both environmental and human health effects. Implementation of novel insight in metrics determining dose-effect responses is obtained via the following objectives:

- Determination of the relationship between external or total administered dose and internal (specific organ dose/environmental species) dose.
- Determination of the dose metric which provides the best descriptor for dose-response relationships as, on forehand, the dose can hypothetically be described by different metrics (e.g. mass, number of particles, volume, surface area, etc.).
- Evaluation of the suitability of the various metrics by assessing the potential of different MNs to provide data for the dose-effect curve.
- Evaluation of possibilities to use in vitro assays for determination and expression of dose-response relationships to obtain insight in dose-metrics and mechanisms of toxicity.
- Investigation of the limitations of the dose metrics. This includes addressing the questions if the dose metric is only suitable for specific responses, for the specific element of the nanoparticles investigated, or related to the characteristics of the nanoparticles at the target site only.

Strategic and innovative aspects

The novelty of the project concerns determination of the ‘best’ dose metric based on the characteristics of the internal dose, as it is assumed that MNs with specific characteristics are preferentially transported to the site where toxicity can occur. Up till now, research on the dose metric of MNs was based on the administered dose of MNs, mainly expressed as mass. However, this approach is limited as it does not take into consideration fate and migration in either humans or the environment, and as it does not take into consideration the inherent size-related properties of MNs.
In addition, the dose metrics for MNs is evaluated for human health *and* environmental endpoints, as similar processes are considered to play a role.
The project is a combination of scientific research, advanced fate and effect modelling, and translation to consequences for integrative risk assessment for a quickly emerging class of chemicals for which, despite considerable research efforts, no overall risk assessment approach is available. The developed dosimetry models and insights gained in dose-response relationships of MNs will steer future risk assessment and will be of importance for both legislators and industry in risk assessment and in risk communication. Society as a whole will

benefit directly from the project as the major outcome will be the foundation for a balanced risk assessment of MNs.

Planned activities

- Preliminary translation to risk assessment. At the start of the project a case study will be performed to identify data currently available for an integrated risk assessment of MNs including, where available the factual use of alternative metrics.
- Evaluation of available data for risk assessment and dose-response modelling for both environmental and human exposure for TiO_2, CeO_2 and ZnO.
- Verification of specifications of acquired nanomaterial. From other research projects studying nanomaterials, it is evident that a limited physical-chemical verification of technical data sheets of the obtained MNs is advisable.
- Environmental research. A quantitative description of the fate of MNs will first of all be developed for each of the environmental media of interest. Ecotoxicological effects will be evaluated based on the effective dose for various environmental species, such as zebrafish, daphnias, algae, plants, and earthworms.
- Hazard identification. In vitro dose-response evaluation and in vivo dose-response evaluation.
- Modelling of dose-response relationships both for environmental and health effects; Translation to risk assessment. The resulting integrative report will be a direct input for the REACH implementation projects, giving direction for future risk assessment of MNs.

Planned products

- Two PhD theses.
- Ten peer reviewed publications.
- Contribution to centralized European databases.

Foreseen follow-up

The improvement in the characterization of the hazard by means of a more specific description of the dose-response relationship will benefit the understanding of the potential risks involved in the use of nanomaterials. This improved insight in the dose response relationship will facilitate the risk evaluation and resulting estimation for both the environment and human health. The results may be used by risk assessors both in governmental and industrial settings.

In addition, it can be foreseen that this insight in dose-response relationship constitutes be a first step to evaluate the possibilities for read across and extrapolation of toxicity data between different types of MNs. When indeed it can be demonstrated that read across and/or extrapolation is possible, be it with certain limitations, this would mean an enormous step forward in the risk assessment of nanomaterials. This would also have a considerable effect on the reduction of the use of laboratory animals for the safety evaluation of MNs.

Title:	**Exploration of the nature, extent and policy relevance of potential ecological effects of radio frequency electromagnetic fields (PEER)**
Project number:	**S/607024**
Project leader:	Prof. dr. ir. W.J.G.M. Peijnenburg MEV-LER)
Start:	01-03-2011
End:	29-02-2012
Total SOR-budget:	€ 92,565

Motivation

Due to increased wireless communication (e.g. mobile phone) and information sharing (e.g. wireless internet), as of the 1990s ambient exposure to electromagnetic field is increasing. Apart from intriguing ongoing discussions on possible adverse effects of Radio Frequency Electromagnetic Fields (RF EMF) on humans, these developments have raised serious concerns of scientists worldwide on possible ecological effects. Adverse ecological effects, often at typical ambient expose levels, have been published in the scientific literature for, among others, reproduction, navigation and coordination for in particular birds, insects, mice and rats. Furthermore, there are several hypotheses and pilot projects from scientists on possible effects of RF EMF on bees, doves and bats. Up till now the possibility of adverse ecological effects of electromagnetic fields on (parts of) ecosystems has received very limited attention. Although possible adverse ecological effects are at present not well studied and understood, it can at this stage not be ruled that there are indeed significant effects on wildlife and economically valuable key species like honeybees.

It is therefore proposed to provide a scientific overview of the nature and extent of the potential ecological effects of RF EMF. This review is not only intended to provide insight on the possible threats for biodiversity, and thus on the relevance of this stressor within Environmental Risk Assessment, but also because factual information on RF EMF impacts on organisms might assist in explaining the potential impacts suggested for humans.

Clearly, only when significant ecological effects have unambiguously been demonstrated scientifically then this issue deserves policy attention in view of the large scale spread of GSM and UMTS (telecommunication systems) transmitters in natural, rural and city landscapes.

Furthermore, laboratory and mechanistic studies on animals and plants are relatively easy to perform compared with human studies, which make biological studies potentially very valuable to investigate effects and mechanisms of RF EMF in depth. In view of current discussions on possible health effects of RF EMF on humans, a clear picture of ecological effects of RF EMF is expected to be of importance for a better understanding of potential effects on humans.

Aim of the project

In view of the considerations given above, the aim of this project is to explore the nature and extent of potential ecological effects of Radio Frequency Electromagnetic Fields. The specific objectives of this project are:

- To perform an extensive and objective review, and analysis of the available scientific literature on the biological and ecological effects of RF EMF.
- To translate the main findings of this scientific review into an advisory report on the ecological effects of RF EMF. Depending on the scientific results, two directions are possible for the second part of this report: to formulate the tentative implications for the Dutch situation for policymaking purposes or to formulate additional research needs, amongst other for inclusion in the European Framework Programme 7/8.

Strategic and innovative aspects
This research field is completely new and unexplored in the Netherlands. In several other countries such as Spain, Germany, Belgium, Sweden and the United States a certain amount of research on ecological effects of RF EMF has been performed, but on the whole this a new emerging field of awareness to both public at large and legislators. This proposal is the first Dutch initiative to find out if RF EMF has impact on organisms. At present it is scientifically unclear if this new theme presents a potential environmental risk and if it needs policy attention in the Netherlands. Based on the scientific review produced in this project, an advisory report will be written with a summary of the scientific findings and, depending on the nature of the results first tentative policy recommendations for the Dutch situation or formulation of additional research needs.

Planned activities
- Collecting information, data overview, gathering meta-study information.
- Criteria analysis and interpretation.
- Implementation of scientific knowledge with experiences in the field (consulting experts, consulting policymakers), writing tentative policy note on relevance and impact of EMF.

Planned products
- A scientific review publication.
- An advisory report containing the main scientific results and, depending on the outcome of the review: tentative recommendations regarding the policy aspects of the results of the review, or additional research needs in this field.

Foreseen follow-up
The knowledge generated within this project will be valuable for future policy advisory projects from the Dutch Ministry of Infrastructure and the Environment (IenM) and the Ministry of Economic Affairs, Agriculture and Innovation (EL&I) (e.g. implementation within Natura2000 projects, and flora and fauna projects from EL&I), landscape planning projects, as well as from the Ministry of Defence.

Title:	**SCARIER?**
Project number:	**S/610004**
Project leader:	Bijwaard, dhr. dr. H. (Harmen) (MEV/LSO)
Start:	01-01-2012
End:	31-12-2015
Total SOR-budget:	€ 600.000

Motivation
Nuclear power carries a small risk for nuclear accidents that may lead to the exposure of large populations to generally low doses of ionising radiation. The recent events in Fukushima, Japan, clearly demonstrate that such risks cannot be ignored even in highly technologically developed countries. The construction of new nuclear power plants possibly in the Netherlands and certainly elsewhere in Europe increase the risk of a nuclear accident. In addition, the continued threat of terrorist attacks with nuclear material in the form of dirty bombs, implies the potential exposure of large city populations to relatively low doses. At the same time regular population doses are on the rise, mainly due to

increasing medical exposures, specifically from Computer Tomography (CT) scans. In the above cases most exposures will fall in the low dose range. Risks from such exposures carry a large uncertainty. Radiation protection authorities therefore take what is generally assumed to be a conservative stand using risks mainly derived from A-bomb exposures. This project aims for reducing the uncertainty in low-dose risks as far as cancer is concerned. Well-defined risks could considerably reduce costs of radiation protection measures and simultaneously guarantee optimal protection of public health, have an impact on medical diagnostic procedures and will therefore interest policy makers.

Aim of the project

The overarching aim of this project is to improve current estimates of low-dose risk and to reduce the associated uncertainties. There are two main reasons why low-dose cancer risks are poorly understood: (1) due to the large background cancer incidence, epidemiological studies that intend to observe low dose effects become prohibitively large, and (2) there are indications, but no universally accepted proofs, that the biological effects of radiation are different at low doses compared to high doses.
The objective of this project is to try to provide a solution to both these issues by modelling: a carcinogenesis model that incorporates the relevant (low-dose) radiobiology can be used to describe cancer incidence or mortality in (manageable) populations exposed to low and moderate doses of radiation. Once fitted, the model can be used to calculate cancer risks for the doses and dose rates of interest. The model will include so-called Non-Targeted Effects (NTE), for which recently new evidence has been obtained. This project will focus on the bystander effect (BE), but may address other NTE if this is deemed relevant and possible. It is not simply aimed at incorporating BE in cancer modelling, but at assessing its relevance for cancer risk. A specific objective of this project will be to develop new cancer models including BE or other NTE, building on pre-existing and successful modelling of two types of cancer: (1) leukaemia, which is intimately related to nuclear accidents and which continues to be a source of anxiety in populations living in the proximity of nuclear power plants, and (2) lung cancer, the cancer with the highest death rate in developed countries, for which in many countries population screening with CT is currently being investigated. Important objectives of this project will be to provide risk estimates of low doses for these types of cancer with and without the incorporation of BE or other NTE, to judge whether NTE are relevant for low-dose risks and to thereby provide better constraints on uncertainties in these risks. The derived models will help, together with more experimental work on in vivo effects, to reach a final verdict on the significance of NTE for low-dose radiation risks.

Strategic and innovative aspects

With new nuclear facilities being planned (both for power generation and for the production of radiopharmaceuticals) and with new plans for radiodiagnostic screening being proposed, knowledge of low-dose risks will become more and more important for the Dutch government. Furthermore, in the aftermath of the Fukushima accident low-dose risks will probably become a prominent issue as they also continue to be 25 years after Chernobyl.

Planned activities

The project will have two major research topics:

- The relation between ionising radiation and leukaemia.
- The risks of CT screening for inducing lung cancer (compared to the benefit of early tumour detection).

For both topics BE and perhaps other NTE mechanisms will be investigated. A go/no go decision is included after a literature study that is aimed at BE, but may incorporate other NTE if these are deemed relevant for low-dose risk estimation. If the addition of probable BE or other NTE mechanisms is not likely to have an added value for low dose risk estimation the project will be discontinued.

Planned products
This project aims for the following (scientific) publications:
- A new lung cancer model including smoking habits and BE/NTE fitted to Hodgkin patient data, indicating the influence of BE/NTE on risk.
- A new leukaemia model including BE/NTE using data from a split-dose experiment, indicating the influence of BE/NTE on risk.
- Estimates of human leukaemia risks using input from animal modelling with relevance to regular and irregular exposures from nuclear installations,
- Comparison of X-ray and radon risks for lung cancer with specific attention to the radiation risks of lung cancer screening.
- Tumour growth models fitted to lung cancer modelling outcomes,
- Review paper on NTE mechanisms and their relevance for cancer modelling.

Foreseen follow-up
Apart from the products that have been identified in the above, considerable follow-up is expected based on experiences in the previous strategic research project. Lung cancer CT screening is currently being investigated in the Netherlands (and elsewhere). This study will shed more light on the radiation risks that are involved. This is important for a complete risk-benefit analysis of this form of screening. In addition, in the current debate on the construction of new nuclear power plants in the Netherlands radiation risks will play an important role, especially after the Fukushima accident. In the aftermath of the Fukushima accident this project will help answering questions about low-dose radiation risks. Results will be disseminated internationally through presentations and papers but most likely also through UNSCEAR, the authorative UN body for radiation effects.
In all probability this project will generate new ministerial assignments related to the proposed expansion of nuclear power. Scientific expertise in this field is essential for RIVM to give authorative support to the Ministry of Economic affairs, Agriculture and Innovation. (EL&I)

Title:	**D-Light&Food** [1]
Project number:	**S/610020**
Project leader:	Slaper, dhr. dr. H. (Harry) (MEV/LSO)
Start:	01-01-2012
End:	31-12-2015
Total SOR-budget:	€ 890.200

Motivation
Vitamin D is crucial for healthy bone formation and therefore contributes to the prevention of rickets and osteoporosis. A causal relationship for a protective role of vitamin D for colorectal cancer is biologically plausible and supported by in vitro and experimental animal work. Moreover, adequate vitamin D levels may

[1] This project is an extension of D-light and food pre, and therefore both projects have identical projectnumbers.

also be associated with a lower risk of other conditions such as cardiovascular diseases, auto-immune diseases, infectious diseases, type 2 diabetes and depression. In summary, adequate vitamin D levels may well provide many additional health benefits in addition to bone health.
Solar UV-exposure in summertime is the major natural source of vitamin D. However, UV radiation exposure has consistently been linked to an increased risk of (both melanoma and non-melanoma) skin cancer (25000 new cases and 700 deaths yearly in the Netherlands) and cataract. Therefore, public health strategies so far primarily focused on reducing UV-exposure to protect against skin cancer and cataract.
Dietary intake is a major source of vitamin D in wintertime, but also winter time vitamin D status might still be partly related to summer time production of vitamin d in the skin. Vitamin D can be obtained from foods like fatty fish, eggs, liver, meat, dairy products or fortified foods and food supplements. Excessive dietary intake of vitamin D leads to problems of the kidney in calcium excretion, in the long term resulting in calcium deposition around the organs.
Thus far in reports on improving vitamin D status the focus was either on improving food-intake or improving UV-exposure habits and a combined and integrated analysis is largely lacking. This project is a first step in bringing both expertise fields together. It should be the first integrative step to a risk-benefit assessment and focuses on identifying main research gaps that should be tackled to improve such assessments. These assessments can help in the development of proper health strategies.

Aim of the project
We aim at an integrated health impact assessment for UV-exposure and vitamin D intake, taking into account present dietary intake levels and exposure habits and knowledge on the health impacts. A framework is developed in which health risks and benefits can be assessed and balanced in a combined analysis of behavioural changes in exposure habits and dietary changes in vitamin D intake. The framework will be used to develop tools/models for risk-benefit assessments and aiming at scenario studies to evaluate the health effects of combined changes in: the UV-radiation environment, behavioural patterns regarding UV-exposure and the dietary vitamin D intake (diet, fortified foods, supplements). Thus, the tools will be used to explore “healthy” UV-exposure and vitamin D intake scenarios to support further development of integrated public health strategies.

Strategic and innovative aspects
A proper comparative assessment of the present contribution of dietary intake and skin production through exposure to UV is not available for the Netherlands. Nutritional research was identified as one of the topics not properly covered in the strategic research agenda from RIVM so far. This project partly fills in that gap, and nutritional vitamin D is generally regarded as a very relevant public health issue.
By bringing together and integrating the expertise from various disciplines ((molecular) biology, biochemistry, epidemiology, nutrition, food consumption, exposure behavior, atmospheric physics, and health impact modeling) this project is an example for an integrative approach for environmental and nutritional health. In view of the large health impacts involved (tens of thousands of cancer cases, and thousands of deaths annually) in the Netherlands) the subject is highly relevant from the perspective of public health. Present pre-existing complementary expertise in three different labs/units is integrated. The follow up research proposed here fills important research gaps identified by the Health Council of the Netherlands but so far not addressed

elsewhere, such as: the determination and assessment of the vitamin D status (through 25-OH-D determinations in blood) in relation to vitamin D intake and UV-induced vitamin D production in the skin, and the balanced risk-benefit analysis. The strategic and integrative research proposed in this project contributes to RIVM's authoritative scientific and supportive role in balancing risks and benefits in the considerations of future policy-options to improve vitamin D status.

Planned activities

The first phase of the project is in 2012 and will focus on the development of preliminary tools/models to calculate vitamin D status in relation to intake and personal UV-exposure.
In addition, methods are tested that can be used in the observational study that is part of phase 2. At the end of 2012 phase 1 will be finalised with a detailed project plan and go no go decision paper for the observational study and further research to be conducted in the integrated assessment in phase 2.
Four work packages (WP) are distinguished.

- WP-A provides the integrative framework of the project and is focused on the overall health impact assessment. The other work packages provide results that will be used in the WP-A.
- WP B extracts, exploits and combines available information from various data sources (outlined in sections 2.2 and 2.3) on vitamin D status, vitamin D intake and UV-exposure in the Netherlands. This will be used to develop a model to predict vitamin D status in relation to vitamin D intake and estimated UV-exposure.
- WP-C is an observational study in the Netherlands to establish and relate personal UV-exposure, exposure behaviour, vitamin D intake and vitamin D status within a group of consented volunteers.
- WP-D aims at an intervention study and requires ancillary budget and/or further collaborations to be established in the course of the project.

Planned products

- Website UV and vitamin D on public dissemination of findings.
- Report/publication on vitamin D status in relation to estimated UV-exposure and vitamin D intake through food and supplements.
- Report/publication on vitamin D intake in the Netherlands.
- Publication on seasonal variation of vitamin D intake in the Netherlands.
- Feasibility report/paper and detailed project plan for the observational study in phase 2. This decision paper should lead to a go – no go decision on the phase 2 activities.
- Report/publication on comparative test of different personal dosimeters
- Publication on personal UV-dosimetry in the Netherlands.
- Publication on relationship between vitamin D status, intake and UV-exposure.
- Improved model for the determination of vitamin D status in relation to UV-exposure en vitamin D intake, to be used in the integrated health impact assessment.

Foreseen follow-up

An international policy debate on how to improve vitamin D status and avoid deficiencies in Europe has al ready entered the political and policy arena in Brussels. In march 2010 members of the European Parliament organized a broad meeting where medical experts and vitamin D experts met with members of parliament on vitamin D. Also WHO/Europe has put vitamin D deficiencies high on their policy agenda. These broad international policy initiatives are likely to further influence the future Dutch policy agenda. KWF/Kankerbestrijding (Dutch cancer foundation) has al ready expressed their great interest in the

debates on vitamin D effects, and the Dutch health council al ready indicated that one of the research priorities in this field would be to establish the relationship between vitamin D status and the production of vitamin D in the skin through exposure to ultraviolet radiation on the one hand and the intake of vitamin D on the other. RIVM has the unique position that it has expertise on both these fields at hand. Results of this project can directly be used to support future policy questions in the Netherlands, and it might well be one of the policy arena´s where new commissions can be achieved in the future.

Title:	**D-light and food pre**
Project number:	**S/610020**
Project leader:	Dr. H. Slaper (Harry) (MEV-LSO)
Start:	01-01-2011
End:	01-04-2012
Total SOR-budget:	€ 105,000

Motivation

Vitamin D is crucial for healthy bone formation and therefore contributes to the prevention of rickets and osteoporosis. More recent, several studies have demonstrated that vitamin D levels in blood are frequently inversely associated with the incidence of major cancers like colorectal, breast and prostate cancer. A causal relationship for a protective role of vitamin D for colorectal cancer is biologically plausible and supported by in vitro and experimental animal work. Moreover, adequate vitamin D levels may also be associated with a lower risk of other conditions such as cardiovascular diseases, autoimmune diseases, infectious diseases, type 2 diabetes and depression. In summary, adequate vitamin D levels may well provide many additional health benefits in addition to bone health.

Solar UV exposure in summertime is the major natural source of vitamin D. However, UV radiation exposure has consistently been linked to an increased risk of (both melanoma and non-melanoma) skin cancer (25000 new cases and 700 deaths yearly in the Netherlands) and cataract. Skin cancer incidences have increased in the past decades, especially for melanoma. The most probable cause is a change in exposure behaviour, over the past 50-60 years (longer summer holidays in southern regions). Further increases in incidence can be expected due to ageing of the population and due to increases in environmental UV radiation caused by ozone depletion and climate changes (observed in the past 25 years).

Dietary intake is a major source of vitamin D in wintertime. Vitamin D can be obtained from foods like fatty fish, eggs, liver, meat, dairy products or fortified foods and food supplements. Excessive dietary intake of vitamin D leads to problems of the kidney in calcium excretion, in the long term resulting in calcium deposition around the organs. In addition, high vitamin D levels possibly lead to an increased risk for pancreatic cancer. It should be noted that only too high dietary vitamin D intake may cause toxic health effects. As, at high UV exposure levels, a natural feedback mechanism in the skin effectively saturates production, preventing toxic levels in the circulation to occur due to UV exposure alone.

It has been suggested that in the Netherlands vitamin D deficiency is widespread at the end of the winter, when UV exposure is very low. Year round inadequate levels are observed in certain subpopulations; subjects with low UV exposure, and or a dark skin type. Central in the debates is how to best achieve and maintain optimal vitamin D levels and not at least, how they are defined.

Aim of the project

We aim at a first step towards an integrated health impact assessment for UV exposure and vitamin D intake. We consider present knowledge on dietary intake levels, UV exposure habits and the health impacts involved, and focus on identifying the main research gaps that limit the development of proper health strategies. Important activities that will be addressed in this pre-study:

- Identify main gaps in the present knowledge that limit the ability to define adequate UV exposure and vitamin D intake strategies.
- Provide an indication of the relative and absolute contributions of diet, food supplements and UV exposure to vitamin D status in the Netherlands using existing information and identifying uncertainties therein.

The results of this preliminary study should enable an outline of further research that is required to develop a framework that can be used to study the balance of the health effects of combined changes in: the UV radiation environment, behavioural patterns regarding UV exposure and the dietary vitamin D intake (diet, fortified foods, and supplements). A follow-up project should then fill in some of the major research gaps identified to improve an integrated risk-benefit analysis.

Strategic and innovative aspects

The question how to best achieve a healthy vitamin D status is presently often addressed from two separate perspectives: focusing on either the required UV exposure, or on nutritional requirements. An integrated approach is needed. By bringing together and integrating the expertise from various disciplines ((molecular) biology, biochemistry, epidemiology, nutrition, food consumption, exposure behaviour, atmospheric physics, and health impact modelling) this project is an example for an integrative approach for environmental and nutritional health. In view of the large health impacts involved the subject is highly relevant from the perspective of public health and the relevance is further strengthened by its link to climate change effects. The outcome of the project should be the first step towards an integrated health impact assessment for vitamin D (both UV exposure and dietary intake).

Planned activities

- Writing of a position paper/report, in which for all vital steps in the integrated risk-benefit assessment the available information and data will be evaluated and important knowledge gaps will be further identified. The strength of evidence and relevance of health effects associated with UV exposure and vitamin D will be identified, the availability of data is explored for e.g. dose-health effect modelling, dietary intake assessment, vitamin D status, UV exposure, conversion to DALY (Daily Adjusted Life Years), and (international) availability of exposure-status models and integrated risk-benefit models for vitamin D. This will result in a more detailed agenda for further research to be performed in follow-up research project(s).
- A final concept of the report will be circulated in a consultation round among researchers in these fields of expertise. Responses of the consultation will be either incorporated into the report or documented in a separate summary

report. In the later phase of the preliminary study a publication will be aimed for.

Planned products
A concept report will be produced that is the basis for the consultation round. The last part of the project will be used to summarize the key results in a final chapter or stand alone conclusion paper. Some of the work performed in this project might well be usable in later publications.

Foreseen follow-up
A risk benefit assessment for UV exposure and vitamin D intake has not been worked out yet for the Netherlands. Proper advice on UV exposure requires additional information on the dependence of vitamin D status on UV exposure and vitamin D intake. Given the fact that a reduction of 30-40% in incidence of colorectal cancer has been reported in relation to high vitamin D levels in blood the public health effects are highly significant. The results obtained within this project give insight in the vitamin D status in the Netherlands and in the characteristics of UV exposure and vitamin D intake. A follow-up study, based on the results of the present prestudy, remains necessary to assess the dynamics between these factors, with the aim to balance health risks and benefits. The framework resulting from pre-study and follow-up can be applied to estimate the balance of health risks and benefits for different potential strategies to improve vitamin D status. These analyses will help to select best practice strategies for UV exposure and vitamin D intake, for different subpopulations. This project is expected to be the no regret first step towards a public health strategy on UV exposure and vitamin D intake.

Title:	**Irradiance**
Project number:	**S/610021**
Project leader:	Dr. H. Bijwaard (Harmen) (MEV-LSO)
Start:	01-01-2011
End:	31-12-2013
Total SOR-budget:	€ 200,000

Motivation
Ionising radiation has been a well-known carcinogen for many years due to the excess cancer cases among the A-bomb survivors. New epidemiological studies of this cohort show that cancer is not the only major, long-term concern: the risk of circulatory, mainly vascular, diseases is increased markedly too, raising the number of long-term casualties by 34%.
Vascular damage was known to occur in high-dose radiotherapy, but most of the A-bomb survivors were exposed to only moderate or low doses.

The new insights into radiation-induced cardiovascular effects call for a reconsideration of risks of low and moderate doses. This is the dose range that is important for radiation-protection purposes, but also for policy decisions regarding, e.g. extended population screening with X-rays or the construction of new nuclear facilities that are currently being planned in the Netherlands. In short: the contribution of (cardio)vascular disease to the long-term radiation risk could change radiation protection measures significantly.
In the low-dose range excess cases of (cardio)vascular disease are extremely difficult to observe against the natural variation in the high background incidence. This implies that epidemiologically derived low-dose risks can only be

obtained by extrapolation from high doses because for lower doses, studies would have to be carried out on prohibitively large cohorts to reach the required level of significance. The systems biological model that is to be developed in this project hopefully provides a better foundation to qualitatively estimate low dose risks, if it correctly incorporates the radiobiological mechanisms that are relevant at low dose. At least, it should indicate where radiation is likely to act for vascular damage and hence guide new experiments.

In 2009 a pilot study was conducted for vascular plaque formation. This demonstrated the feasibility of the proposed modelling: the different actions of radiation can be combined in a mathematical description. In this description radiation initially causes endothelial damage leading to an inflammatory response. Here, radiation can act through oxidation of Low Density Lipoprotein (LDL)-cholesterol and activation of certain cell surface proteins, both of which play a role in fatty streak formation. In the transformation of the fatty streak to a plaque, radiation may stimulate clonal expansion of smooth muscle cells that form the fibrous cap. Radiation can thus, in theory, act in several stages of plaque formation. This model provides a starting point for this project.

Aim of the project
The focus of this project will be on contributions of radiation to risks of vascular effects. In order to achieve this, a biologically motivated mathematical model for vascular effects of radiation will be developed. The initial aim for the vascular model will be to qualitatively reproduce the observed plaque formation in arteries of exposed laboratory mice. From thereon, the implications for man will be investigated.

Strategic and innovative aspects
In the Netherlands RIVM is the only party involved in modelling low-dose effects. The project is important for maintaining the scientific knowledge base of RIVM, which focuses its activities around ionising radiation and potential nuclear emergencies. As (cardio)vascular disease risk is likely to play an important role in radiation protection in the coming years, this project should provide the knowledge base to become authoratative in this particular part of the radiation protection field. In this way we will be better prepared to serve the Ministry of EL&I (Economic affairs, agriculture and innovation) when questions on this topic arise or policies need to be formulated.
In this field RIVM is a relatively small stakeholder on an international scale. Through this project access is gained to international radiation research (from larger stakeholders).
For example, the project will facilitate the connection to the Low-dose ionising radiation investigation consortium of the Netherlands (LIRICS), which is a member of the Multidisciplinary European low dose initiative. Knowledge and expertise gained through these connections will help in supporting the Ministry of EL&I.

Planned activities
- Refine the mathematical description by further exploring the scientific literature on this subject and through our collaborations with the Netherlands Cancer Institute (NKI).
- An informed decision on a coding platform (computer language) will be made and the implementation of the mathematical model in computer code will be started.
- The computer model will be matched to the NKI animal data and possibly to newly performed experiments within EU projects. As our model will

incorporate the effects of ionising radiation on the different steps in the plaque formation process, it could provide input for experiments that show where radiation acts in reality.

Planned products
- Knowledge of low-dose vascular damage development. More tangible products will comprise a mechanistic vascular damage model and, more importantly.
- Two scientific publications.

Foreseen follow-up
Cardiovascular effects of ionising radiation are likely to become more and more important as the Dutch population is aging and the numbers of diagnostic CT-scans, but also of therapeutical radiation treatments are rising. Multiple diagnostic scans quite often lead to cumulative doses > 100 mSv (millisievert). In radiation therapy (cardio)vascular complications already are quite common. It is likely that vascular effects will need to be incorporated in radiation protection measures. Expertise on this topic is important for RIVM to be able to support the Ministry of EL&I when questions arise or policies need to be formulated.

Title:	**ENPRA**
Project number:	**E/630017**
Project leader:	Gosens, mw. dr. I. (Ilse) (MEV/ MGO)
Start:	01-05-2009
End:	31-10-2012
Total SOR-budget:	€ 70.000

Motivation
The SOR Science budget will be used as part of the co-financing that is needed to perform the work that is foreseen in workpackage 5 of the overall ENPRA project. In this workpackage, animal studies are performed to make a hazard assessment of a panel of nine different nanoparticles. The hazard assessment forms the basis of the choice of material that will be used in other tasks within WP5 by other partners. In addition, the data from the hazard assessment will be used in the toxicological risk assessment that will be performed at the end of the project by partners in work package 6.

Aim of the project
Perform a hazard assessment for acute toxicity for a panel of nine different engineered nanoparticles by making dose-response curves for three different endpoints after administration via the inhalatory route. The focus will be on effects on the lung, liver and cardiovascular system.

Strategic and innovative aspects
The hazard assessment is of vital importance for the rest of the project, since other partners will base the choice of materials on this for their specific tasks within the project. More importantly, it will make up an essential part of the risk assessment of engineered nanoparticles, the overall goal of the project.

Planned activities
- Execute experimental study in mice August-September 2011.
- Analyse organs, blood and lung lavage samples for adverse effects due to nanoparticle exposure October 2011.

- Make dose-response curves with statistical program PROAST November 2011.
- Prepare concept for publication on hazard assessment December 2011.
- Explore possibilities to write second publication on the experimental design for ZnO toxicity testing January 2012.
- Finish writing publications and end of project October 2012.

Planned products
- Peer reviewed publication describing the hazard assessment of a panel of 9 different particles.
- Possibly a second peer reviewed publication: short communication on the experimental design to test the toxicity of ZnO particles in collaboration with the NRCWE (Denmark).

Foreseen follow-up
The scientific community will profit from the results, since information on the toxicity of these type of materials is currently a hot research topic.
EU citizens will profit, since these results will be used as one piece of information that is needed to make a risk assessment for engineered nanoparticles.

Title:	**Oxidative potential exposure and risk assessment (OPERA)**
Project number:	**S/630021**
Project leader:	Dr. N. Janssen (Nicole) (MEV-MGO)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 842,000

Motivation
Indoor and outdoor air pollution consists of complex heterogeneous mixtures of gases, vapours and aerosols including varying particle sizes and a wide range of chemical components. Outdoor air quality is controlled by setting standards for specific gases and particulate matter (PM). In other settings, risks are generally also evaluated and controlled using standards for specific substances, such as threshold limit values (TLV) for the workplace and Acute Exposure Guideline Levels (AEGLs) for emergency response. All these standards ignore the fact that exposures occur as mixtures and the interaction of components that may cause different and synergistic effects. It would therefore be of major interest to develop a health relevant indicator that can integrate the toxic properties of the air pollution mixture. This project aims to evaluate such an indicator, with a focus on the PM fraction of air pollution.

In recent years, numerous toxicological studies have documented the capacity of inhaled PM to cause oxidative stress within the lung, as well as systemically, and related this capacity to the health effects observed in exposed subjects. Oxidative stress is also well accepted as a mechanism that could explain cardio respiratory effects observed in epidemiological studies. The oxidative potential (OP) of PM has thus been proposed as a health relevant indicator that could be more informative than mass alone and could be used to monitor the air quality. Despite that toxicological information supports the choice of OP as an indicator, actual application in epidemiological studies is limited. This is partly due to the fact that several assays are available to quantify OP and it is not clear which assay is the most suitable as assays respond preferentially to a wide range of

components (e.g. metals, organic components). Also, little is known about the various aspects that affect PM during the full chain, from origin at the source to concentrations, exposure and actual health effects.

Aim of the project
The aim of this project is to evaluate the value of OP as a biological and health relevant PM metric for air quality assessment and regulation. This concerns both its value as a complementary and as an alternative metric next to PM mass standards.
Specific objectives are:
- To identify the preferred (set of) OP assay(s) for air quality assessment and regulation.
- To evaluate the value of OP as an additional/alternative health relevant air quality indicator throughout the full chain from source to health effects.

Strategic and innovative aspects
The study is innovative in the sense that we will apply a full chain approach to critically evaluate a promising toxicologically based PM metric, including application in epidemiological health effects studies. Also, we will evaluate the added value of this metric from different perspectives (general outdoor air quality, indoor settings and emergency response function). A full chain approach will be applied integrating aerosol physics, exposure assessment, toxicology, epidemiology and HIA. Finally, the efficient use of already existing material allows us to create a large database of OP results at relative low costs.

Planned activities
The project will be conducted in three phases.

Phase 1: Method comparison
The objective of this phase is to define the preferred (set of) OP assay(s) for air quality assessment and regulation, that will be used for further evaluation in the project.
- Selection of a variety of samples from the sets of filters that are available for further analyses in phase 2. In total 160 samples will be selected, representing various sources and mass loadings.
- Data analysis and evaluation: we will compare the four assays in terms of methodological characteristics and ability to distinguish between samples with documented contrasts in composition or toxicity.
- We will assess the correlation among the different OP measures, and their relation to PM mass. Results will be used to select the preferred (set of) OP indicator(s) for the continuation of the study.
- Organization of an international workshop.

Phase 2: Full chain approach
A comprehensive assessment needs to be made at all parts of the causal chain. In this project we will evaluate the value of OP for assessing sources, ambient concentrations, exposures (indoors) and resulting health effects. These aspects will be integrated to assess the value of OP as a potential indicator for air quality.
- Source emissions: to characterize and compare the OP from a wide variety of sources. We will analyse previously collected, and partially chemically characterized, samples from various sources.
- Assessment of spatial and temporal variation in outdoor air.
- Exposure: because people spend a large fraction of their time indoors, it is important to assess the relationship between outdoor and indoor OP.

- Health effects: at present, there is limited epidemiological evidence on the relation between OP and adverse health effects. We will focus on assessing effects of long-term exposure, because for PM these effects have been important in HIA and standard setting.

Phase 3: Overall assessment
The objective of this phase is to conduct an overall assessment of the value of OP compared to PM mass concentrations.
- In this assessment, results from the various activities in the OPERA project will be integrated to assess whether it is valuable to propose OP as a complimentary or alternative air quality indicator.
- Specifically, we will evaluate the performance of the assay(s), the spatio-temporal variability of outdoor concentrations, indoor-outdoor relationships and the relation of OP with cardio respiratory mortality and childhood development and respiratory health.
- An international workshop will be organized.

Planned products
- PhD thesis.
- Seven publications in international scientific journals.

Foreseen follow-up
The proposed study will provide insight in the added value of OP as an additional 'biologically active' metric for air quality. This insight may be used in setting biologically more relevant standards, guideline levels and /or limit values. Identification of an integrated toxicology based indicator will also support more effective abatement strategies via identification of the most toxic sources. The Dutch Ministry of Infrastructure and the Environment (IenM) is showing increasing interest in assessment of additional indicators that are more closely connected to health effects compared to PM mass. In a recent expert meeting on this topic, organized by IenM, OP was identified as an interesting option that needs to be more extensively studied in health effect studies. Availability of an integrated umbrella indicator is also highly recommended for evaluation of indoor air quality. It is anticipated that other ministries may also be interested in the results of this project. The project can therefore lead to new assignments in this area.

Title:	**Healthy action**
Project number:	**S/630022**
Project leader:	Ir. H. Kruize (Hanneke) (MEV-MGO)
Start:	01-01-2011
End:	31-12-2012
Total SOR-budget:	€ 150,000

Motivation
A healthy living environment is an environment that makes people feel well and relaxed, that promotes a healthy lifestyle, and in which pressure on health is as low as possible. It includes both social and physical elements that interact with each other. In this project we focus on the physical environment, and use the broad World Health Organization (WHO) definition for health, including human well-being. Several Dutch ministries (the Ministry of Infrastructure and Environment; the Ministry of Health, Welfare and Sport; the Ministry of the Interior and Kingdom Relations; the Ministry of Economic Affairs, Agriculture and

Innovation) show interest in creating a healthy living environment. As captured in the Dutch policy guideline on environment and health policy priorities 2008-2012 ('Nationale Aanpak Milieu en Gezondheid 2008-2012'), these ministries facilitate and stimulate local authorities to create a healthy physical environment by developing guidelines, tools, databases and overviews of interventions ('good practices') in which the physical environment is adapted to improve health. In addition, local authorities often approach RIVM for information what interventions are most effective. However, most of the available Dutch environmental interventions in which the physical environment is adapted to improve health are not evaluated. Therefore it is not known how effective they are in improving health of the targeted population, and if they have unexpected side effects, potentially resulting in expensive ineffective interventions with unwanted side-effects. Evaluating interventions in the physical environment to improve health require more complex approaches than evaluation of most lifestyle interventions. Many individual and contextual determinants may affect health, and many developments take place in the targeted physical environment simultaneously. Knowledge of the causal mechanism from exposure to health and information on the context in which the intervention takes place is essential. Moreover, vulnerable groups need specific attention, since they may benefit from environmental interventions more than others. In addition, specific attention will be paid to potential side effects on other policy domains. Definition and selection of useful indicators for this type of interventions is therefore an important part of this project. Although each intervention may require specific indicators, it will be attempted to define a core set of indicators. There is no standard methodology for this type of evaluation as yet, but existing initiatives such as the Admission System for best-practice health promotion interventions of the RIVM Centre for Healthy Living (CGL) and Netherlands Youth Institute (NYI) provide a good starting point for this project.

Aim of the project

This project aims to develop a systematic, robust and thorough method to evaluate environmental interventions in which the physical environment is adapted to improve health. There will be in particular attention for:

- Selection of indicators (output, intermediate, context, process).
- Vulnerable groups.
- Potential positive or negative side-effects of the interventions.

This method will be applied on earlier identified interventions in the Netherlands. The evaluated interventions will be put into a (possibly existing) web based database that is open for the public, in order to facilitate policymakers looking for effective interventions to create a healthy living environment, and will potentially be implemented into the admission system and i-database of the RIVM's Centre for Healthy Living (CGL) and Netherlands Youth Institute, that will also serve as an important starting point for this project.

Strategic and innovative aspects

As far as we know there is no standard method available for evaluating interventions in which the physical environment is adapted to improve health. Furthermore, there is no overview of evaluated, effective interventions of this type available for those who want to create a healthy living environment. By using existing experience within CGL and learning from their system, application of the conceptual knowledge on healthy environment and on integrated risk assessment of environment and health from different divisions of RIVM and PBL Netherlands Environmental Assessment Agency (PBL), and by using available

information on 'good practices' in this field collected in other RIVM projects there is a good starting point for this project.

Planned activities

- Literature review and interviews with experts in order to produce an overview of existing evaluation methods and conceptual frameworks of interventions in the field of environment and health, and their pros and cons in the context of this project.
- Workshop with (inter)national experts and policymakers to discuss specifications of the evaluation method.
- Development of the evaluation method, with specific attention for output indicators, vulnerable groups, potential positive or negative side-effects of the interventions, and assessment of effectiveness of integral policy.
- Exploring the possibility to fit the method in the Admission system of CGL and Youth Health Institute.
- Making an overview of existing inventories of interventions adapting the physical environment.
- Interviews with experts and policymakers to gain insight into other examples, particularly of intersectoral policy (e.g. the policy approach used in the 40 'Krachtwijken'), and synergy/counteractions in this policy.
- Collection of additional required information not directly available from the available interventions.
- Testing of the method on a subset of collected interventions and practices to evaluate their effectiveness.
- Adaptation of the method based on the experiences on this testing.
- Depending on the results and findings, integration of the method in the criteria of the Admission system for continuous assessment of local interventions aiming to create a healthier living environment.

Planned products

- Two peer reviewed publications.
- Method to evaluate interventions.
- Database with a first overview of effective of interventions and good practices to create a healthy living environment.
- Paper for Dutch journal.

Foreseen follow-up

This project facilitates authorities to evaluate their interventions and delivers insight into efficient application of interventions to create a healthy local environment.
The evaluation method will potentially be integrated in the admission system of the Recognition Committee of CGL and National Youth Institute (NIY) and be presented in the portal 'Loket Gezond Leven'.
It may also be of use for the manual 'Healthy municipality' ('Gezonde gemeente') of CGL that contains information on how to develop integrated healthy policy and how to create a healthy environment. For this manual there is a great need for information as produced by the proposed project.

Title:	**Investigating the role of individual attitudes in deciding about uncertain risks: a methodology (IRIDIUM)**
Project number:	**S/630023**
Project leader:	Dr. A.B. Knol (Anne) (MEV-MGO)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 726,500

Motivation
Environmental health problems are often complex, large-scale and uncertain. Examples of such 'systemic risks' are climate change, electromagnetic fields (EMF) and nanotechnology. The uncertainties inherent in systemic risks provide leeway for different appraisal of risks: how bad is this? should we intervene? or should we await more information? The interpretation of these risks depends on who you ask: policymakers, scientific experts or the general public.

In order to support decision-making about systemic risks, integrated environmental health impact assessment (IEHIA) is being developed. IEHIA aims to assess environmental health-related problems in ways that take account of complexities, interdependencies and uncertainties. The execution of IEHIA, the interpretation of results and the subsequent decision-making all involve a normative component: they are influenced by the different perspectives of scientists. Similarly, the policy development process can be affected at many phases by the policymakers' perspectives. The appraisal of uncertain risks can thus hardly be called 'objective'. The acceptance of policy measures in the general population is in turn influenced by their perspectives.

If scientists, policymakers and other stakeholders have different perspectives, this can lead (at least) to confusion about why certain policies are implemented, or why certain scientific advice seems to be ignored; and (at worst) to a lack of support for policies or distrust in science. Research on the consideration of different expert roles has remained largely theoretical in the context of environmental health research and policy. Much can be learnt from disciplines such as social psychology and contemporary political science.

Aim of the project
The primary question we address is: What is the role of various perspectives in determining how experts with specific roles appraise environmental health risks and interventions?

We aim to explore which attitudes towards environmental health risks are specifically relevant for the appraisal of environmental health risks; and assess whether these attitudes differ within and between groups or individuals.
Our objective is to create awareness among the scientific and policy community and improve knowledge about the role and potential effects of attitudes on environmental health science and policymaking. In the long run, our study will improve the practice of policy-relevant environmental health research; support the uptake of scientific information in the decision-making process; show ways to increase public support for environmental health interventions; and improve the communication of scientific advice to policymakers and citizens.

Strategic and innovative aspects
Even though the potential roles of experts in appraising uncertain environmental health risks are increasingly acknowledged, as yet there is insufficient knowledge and awareness about the potential effects of these different roles on scientific advice and policymaking, and there are no common methods to assess which underlying perspectives are relevant. Few theories have been validated or operationalized. This makes our research very innovative in the field of environmental health science. The project may lead to new assignments from Dutch ministries or international organizations.

Planned activities
- Literature review about the different roles of scientific experts in providing policy advice and the underlying attitudes and perspectives, related to environmental health risk appraisal.
- Workshop with 'Advisory Board' experts in the field to discuss the latest insights and a 'User Group' with scientists, policymakers and other stakeholders that deal with scientific policy advice or policymaking on uncertain environmental health risks; Case studies.
- In-depth interviews.
- Optimized Q sort.
- Multicriteria analysis.

Planned products
- Guidelines for scientists.
- Q sort method.
- An operational multicriteria analysis module to policy decisions.
- Five peer reviewed papers.

Foreseen follow-up
This work will benefit scientists who communicate uncertain scientific results to policy. It will enhance their understanding about the effects of personal attitudes and perspectives, and provide support for incorporating these insights in the practice of assessing risks and communicating results. Policymakers will similarly benefit from this project, by gaining more insight into the underlying attitudes incorporated in scientific policy advice, the ways to deal with that, and the ways to develop effective policy measures that relate to the attitudes of the population. RIVM as an institute will benefit from the results by receiving credit for taking up a challenging topic which has been on many agendas for a long time, but has thus far been given too little attention.

Title:	**Characterization of idiopatic environmental intolerances (Chi2)**
Project number:	**S/630024**
Project leader:	Dr. I. van Kamp (Irene) (MEV-MGO)
Start:	01-01-2011
End:	01-05-2012
Total SOR-budget:	€ 149,700

Motivation
Idiopathic environmental intolerances (IEI) is a term coined by the World health organization (WHO) to describe a complex (syndrome) characterized by diffuse symptoms reported after exposure to low doses of often everyday environmental factors. The attributions to environmental agents/stressors may have some

causal foundation, but often it is concluded that there is no scientific basis for a causal mechanism and nocebo responses and stress-related somatic attribution are generally assumed to be the main basis for IEI. Manifestations of IEI vary, with common manifestations as sick building syndrome, multiple chemical sensitivity, chronic fatigue, etc. Currently, attribution of IEI to electromagnetic fields, often referred to as hypersensitivity to electricity, is increasing in the Netherlands, and it is expected that (a substantial) part of the health problems attributed to living in houses with balanced ventilation systems are founded in somatic attribution, and thus IEI. Earlier, nutritional aspects and consumer products were implicated, e.g. food colorants (e-numbers) in relation to behavioural problems in children. It is only a matter of time before 'social rippling effects' in the Netherlands will call our attention to claims that vaccination, e.g. Humane papillomavirus (HPV) or swine flu vaccine, has caused a set of non-specific health complaints, i.e. syndromes similar to IEI. The same mechanism is possible in relation to early vaccination and vaccination during pregnancy against swine flu. It is therefore of the utmost importance that RIVM prepares itself through a serious research effort in IEI for a response to such signals.

Aim of the project

The aim of this project is to explore the feasibility of a study to develop and apply tools to characterize Idiopathic (Environmental) Intolerances (IEI), which combine self report methods and diagnostic interviews with state of the art physiological measures (-omics and other biomarkers of exposure).

Specific objectives are to:

- To study theories and evidence regarding IEI across a broad range of environmental exposures, and its underlying cognitive, neurological, psychological and biological mechanisms.
- To inventory the usefulness of single physiological markers and omics in relation to a IEI and a range of environmental exposures.
- To study the mechanism of symptom development in different sensitivity/IEI groups attributing their symptoms to a range of exposures (war veterans, post-traumatic stress disorder (PTSS) patients, electromagnetic fields (EMF), sick building syndrome).
- To discuss the need, value and feasibility of the development of an integrated assessment instrument to measure psychological, physiological and social aspects of IEI with a multidisciplinary team of specialists.

Strategic and innovative aspects

The effort to characterize IEI across different domains and determinants is new; previous research has focused primarily on single manifestations and single determinants. Furthermore, so far there has been little connection between symptom reporting and physiology of IEI. The possibilities of new alternative methods of biomarkers of exposure such as the high throughput screening techniques (HTST) approach have not been explored extensively as yet. Better characterization of a broadly defined syndrome as IEI is needed and societal developments warrant exploration of these new approaches. In this day and age, a statement that 'there is no scientific evidence' without a serious designated research effort in IEI is simply unacceptable. Knowledge about the true nature of IEI will facilitate development of new (societal) action perspectives. Finally the project will make a start with network forming around this highly multidisciplinary theme.

Planned activities
This project is an effort at integrated risk assessment, as it aims to integrate knowledge from different domains and determinants relevant to IEI. Specific aim hereby is to study the feasibility and added value of integrating screenings techniques such as -omics and HTST with single biomarkers and self report measures into one assessment instrument of IEI. If this is the case, a follow-up study around this theme will be recommended. Taking this as a point of departure the study consists of four main elements and phases:

- A literature review.
- Two expert meetings.
- Focus group discussions among different groups diagnosed with IEI both live and web based aimed at onset of symptoms, social context, medical consumption, MHW, health beliefs, personal characteristics, information search behaviour etc and finally.
- A canvassed design of a study into the psychological, social and physiological aspects of IEI and their interplay, and the development of a tool based on this.

Planned products

- Presentations at international conferences.
- Peer reviewed (international) journal article.
- Optional (dependent on the outcomes of a review, expert meetings and focus group discussions) a recommendation for follow-up and a canvassed design of such a larger scale study into the theme.
- The development of a multidisciplinary international network around IEI characterization.

Foreseen follow-up
This feasibility study will lay the ground for a more extensive study into the possibility to develop tools to characterize Idiopathic Environmental Intolerances which combine self report methods, interviews with state of the art physiological measures (-omics' and other biomarkers). The project will take away at least part of the uncertainties regarding IEI and non specific symptoms in different domains.

Several aspects of the project are relevant to other Strategic research Themes (SOR) of the programme. In particular, to Healthy Aging (HEA), since the prevalence of non specific physical symptoms is high, IEI has a serious detrimental effect on quality of life and requires a substantial effort of our health care system. Moreover, the project fits well in filling the gap: from knowledge to action (FKA), since knowledge about the true nature of IEI will facilitate development of new (societal) action perspectives.
Also, the project has relevance to application of new technologies (ANT), since the characterization of physiological aspects of IEI will involve 'omics' and other high-throughput biomarker assays. It will create a base for further international harmonization of characterization of IEI and tool development for which additional financing will be sought and this way enable to better advice professionals from different domains as well as professionals in the field of health promotion and health care.

Title:	**Knowledge integration by physiologically based pharmacokinetic (PBPK) modelling**
Project number:	**S/660021**
Project leader:	Dr. C.C. Hunault (Claudine) (MEV-VIC)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 809,000

Motivation

Providing clinical information on the toxicity of hazardous chemicals in humans in emergency situations is not straightforward. Examples of plausible incidents are acute pollution of drinking water or acute contamination of the food chain with hazardous chemicals. One major obstacle is that human data on toxicity of chemicals are scarce because conducting human studies on hazardous chemicals is not ethical. Fortunately, data on the toxicity of chemicals are available from animal and in vitro studies, and from accidental chemical exposure of humans, although, in the latter, the information on exposure assessment is scarce. These results, however, must be extrapolated for a proper human health assessment. A second obstacle is that individuals present different susceptibilities to hazardous chemicals. The exposure to low doses of chemicals can be non toxic for the general public but toxic for more vulnerable categories of the general public.
In these specific categories, the exposure can interact with the effects of another drug given concurrently (xenobiotic medicine interaction) or can occur at a critical period of development (effect of ageing, pregnant women).

Numerous Physiologically based pharmacokinetic modelling (PBPK) models have been developed for specific chemicals but are not being used in emergency situations. In emergency situations there is usually no time to take stock of the available PBPK models or to adapt existing models to the specific situations of the incidents. Also, generic PBPK models exist, sometimes developed for specific families of compounds according to the physicochemical properties of the chemical (e.g. water soluble /lipophilic or volatile /non-volatile) or for possibly more vulnerable individuals like children or pregnant women. However, the applicability of these generic PBPK models in emergency situations has not been studied yet and only a few of them have been validated in humans. It is therefore necessary to make an inventory of the models relevant to hazardous chemical incidents, to study their applicability in emergency situations, and to promote their implementation in order to better determine and characterize risks from exposure to hazardous substances in acute chemical incidents.

Aim of the project

The aim is to integrate PBPK knowledge in the practice of clinical toxicology in order to be better prepared for acute response in cases of incidents with hazardous chemicals.
The objective is not limited to the development of one model but more generally to practice PBPK modelling in order to use up to date advances in animal and in vitro research. By using the most recent development in PBPK modelling, the National Poisoning Information Centre (NVIC) is better prepared to predict toxic effects and to plan follow-up after chemical incidents. The specific objectives of the project are:

- To put existing PBPK into practice of emergency response strategy.
- To study whether existing models previously developed could be adapted.

- To identify possible risk factors of physical health complications after an incident.
- To identify vulnerable groups for monitoring after the accident.

Strategic and innovative aspects
This project is unique and innovative because it aims at applying existing models in acute chemical incidents. Existing PBPK models are not used in emergency situations because they are too complex or developed using in vitro or animals' data and have not been adapted to and validated in humans. Until now, PBPK modelling has mainly been used in risk assessment of long term exposure to chemicals. PBPK modelling will be used as a tool realizing the synthesis of multiple factors, including factors related to ageing and co-administration of xenobiotics to provide more accurate estimations of the pharmacokinetics of chemicals within the body. It will also help identify the most vulnerable people in need of close monitoring after an incident.
This project is also innovative in the way that it aims at validating PBPK models. Many model parameters are developed from in vitro data or extrapolated from other species, but the final model is used for human risk assessment. Thus for true model validation, human in vivo data are most appropriate.

Planned activities
This project includes four distinct phases of research:
- Making PBPK models operational. Using data of hazardous chemical incidents, including MOD (RIVM's Environmental Incident Service) reports, existing PBPK models will be used to perform simulations; predicted and measured blood concentrations will be compared.
- Prospective collection of in vivo data in humans (e.g. acute and/or chronic intoxications) through prospective observational studies and/or experimental studies.
- Complementary adaptation of the models based on insights provided by the in vivo studies.
- Validation of the resulting PBPK model(s) using data from the literature similar to the daily practice of the NVIC/MOD of the National Institute for Public Health and the Environment.

Planned products
- Improved PBPK models to provide more accurate predictions of xenobiotic deposition in the human body.
- International publications in peer reviewed journals.
- PhD thesis.

Foreseen follow-up
Decision-makers, rescue teams, health professionals and MOD will profit from more accurate advice from NVIC. Integration of knowledge on PBPK modelling will enable providing the best clinical toxicological advice in emergency situations and identifying the most vulnerable people in need of close health monitoring after an incident with hazardous chemicals.
Furthermore, the experience and knowledge acquired through this project will help in optimal planning of disaster relief.

Through this project, the department will benefit not only from increased insight in PBPK modelling, but also in pharmacokinetics, drug-drug interactions, and individual susceptibility. This expertise within our department will support and facilitate the design of future research with the same partners -the other RIVM departments, the Institute for Risk assessment sciences (IRAS) - or new partners - like the Netherlands Forensic Institute (NFI) or medical departments

of the University Medical Centre Utrecht - in the domain of clinical toxicology and on issues concerning risk assessment in public health.

8 Strategic Vaccine Research (SVR)

8.1 Strategic aims

Societal impact
Since the invention of the vaccine against smallpox in the middle of the nineteenth century,
the development of vaccines has increased dramatically. Its impact on public health is tremendous and Dutch society assumes that a number of infectious diseases that were lethal in earlier times now barely exist. There is a long-standing belief that infectious diseases have been defeated. However, this is far from the truth. Only a few diseases have been completely eradicated worldwide. Although many of the remaining pathogens are largely under control due to an effective prevention programme, a constant state of alert is necessary. Pathogens are able to adapt to environmental conditions and may therefore become insensitive to the immunity evoked by the adopted vaccine, rendering vaccination ineffective. Man and his environment also change, influencing the effects of vaccines. A response from vaccinology is therefore essential in order to maintain control of infectious diseases in the future. Improvements of vaccines are also necessary to minimize side effects and to improve dosing techniques. Vaccinology knowledge is not only relevant for infectious diseases, but it also applicable to chronic diseases such as Alzheimer and Parkinson. These diseases are a threat to an ageing population, and there is currently no cure for these diseases. Increased mechanistic knowledge may result in improved prevention and curability of these diseases.

Description and impact in relation to RIVM tasks
The targets of the SVOP (Strategic Vaccine Research programme) were set during the period that vaccine research was carried out by the NVI (Netherlands Vaccine Institute).
NVI's public tasks in vaccine research have been merged with those of RIVM (National Institute for Public Health and the Environment) since January 1st 2011. Consequently, RIVM now has a second strategic research programme, which will merge with the existing Strategic Research RIVM (SOR). For the time being, the SVOP is regarded as the seventh research theme within SOR. The goal of SVOP is to perform scientific research aimed at acquiring public knowledge and innovative concepts from different vaccinological disciplines. This knowledge will be applied to RIVM's public tasks in the vaccinology domain. RIVM advises the Ministry of Health, Welfare and Sport, the International Vaccine Outbreak Team, the Health Council, the World Health Organisation, the International Vaccine Institute and the European Vaccine Initiative with respect to vaccines and vaccine strategies.

The Ministry of Health, Welfare and Sport commissions RIVM to perform vaccine research and related tasks. RIVM actively contributes to world healthcare by transferring vaccine production technology to developing countries to enable local vaccine production. Because of its particular focus, the SVOP is less RIVM-wide oriented than the other research themes. However, its implementation will not be limited to that part of the RIVM organisation originating from the former NVI (Netherlands Vaccine Institute). The SVOP has direct relations with other research themes, such as Healthy Ageing and Dynamics of Infectious Diseases.

Focus and future direction of projects
The aim of the Strategic Vaccine Research Programme (SVOP) is to contribute to the future renewal of vaccines and vaccination strategies, and to develop basic vaccinological knowledge and platform technologies that may enhance this renewal. Knowledge of immunological mechanisms (vaccine immunology) or Correlates of Protection (CoP) will support the innovation of vaccines and vaccination. In addition, cross-border research in the area of vaccine technology, such as research into new needle-free dosing methods, or universal process technology for viral or bacterial vaccines, is regarded as scientifically innovative and strategic vaccine research.

SVOP includes three sub-programmes, namely:

1. Innovative vaccine concepts

This sub-programme focuses on the initial design of innovative vaccine concepts in order to find an answer for emerging infectious diseases, such as the Respiratoir Syncytical Virus in elderly people, tuberculosis, and infirmities of old age like Alzheimer. Research into new dosing systems will also be carried out. The translation of concepts proven to work on a small scale in laboratory animals will continue beyond the scope of SVOP.

2. Vaccine immunology

Effective vaccines may also show side effects. Vaccine development focuses on producing effective vaccines with a minimum of side effects. Mechanistic knowledge is necessary in order to achieve this. This implies knowledge on the effective activity of specific components of vaccines, but also knowledge of adjuvants (auxiliary substances), dosing methods and CoP. Moreover, appropriate animal models to test vaccines will have to be developed.

3. Vaccine technology

The development of a new vaccine is a complicated and time-consuming process. It takes years before a new vaccine can actually be applied. Reducing this time is important for public health. Research into new and widely applicable analysis and process technologies that may enhance the introduction of new vaccines is of utmost importance.

SVOP projects have to fit into one of these sub-programmes.

International connections
Vaccine research has gained a higher priority over the last five years in international bodies such as the WHO and the European Union (EU). This is due to the increased globalisation and the vaccine specific commitment of the Gates Foundation in Global Health.
Both organisations regularly call for research project initiatives within the vaccinology domain. The WHO places calls through the WHO Initiative for Vaccine Research (IVR), and the WHO Department of Public Health, Innovation, Intellectual Property and Trade (PHI), while the EU places calls through the European Commission (EC), namely DG Research and DG Sanco, and in particular the European Centre for Disease Control (ECDC). It is anticipated that SOR co-financing will lead to an increase in internationally oriented vaccinology projects.

Key words
Microbiology, virology, vaccine immunology, adjuvants, alternative dosing methods, vaccine development, CoP, vaccine technology, bacterial vaccines, peptide vaccines, viral vaccines, platform technology

8.2 List SVR

Number	Title	Project leader	Int.
S/000083	Innate immunity receptors	Peter van der Ley	
S/000102	Innovative synthetic vaccines: a peptide vaccine against Alzheimer's disease	Peter Hoogerhout	
S/000105	Plaform technology for viral vaccines	Wolfried Bakker	
S/000191	Immunoproteomics	Ad de Jong	
S/000192	Alternative vaccine delivery	Pierre Amorij	
S/000193	Immunological programming	Wanda Han	
S/000206	Q fever vaccine based on heterologous expression of O antigen	Peter van der Ley	
S/000207	Recombinant live attenuated RSV vaccine for the elderly	Teun Guichelaar	
S/000220	Vaccinomics: systems biology and vaccinology, molecular signatures of pertussis vaccination	Bernard Metz	

Int. = international project cofinanced by SOR-budget

8.3 Summaries

Title:	**Innate immunity receptors**
Project number:	**S/000083**
Project leader:	Ley, dhr. dr. P.A. van der (Peter) (CIb/VAC/VR)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 2.658.179

Motivation
Adjuvants are needed in vaccines to obtain efficient immune responses. A greater mechanistic understanding of adjuvants in vaccines allows the design of adjuvants tailor-made for specific vaccines and/or routes of immunization, and with a better ratio between effectivity and reactogenicity.

The immune system can be divided into the relatively non-specific rapid response innate immune system, and the more slowly developing but specifically targeted adaptive immune system. Traditionally, most immunological research has been directed at the latter, but in recent years understanding of the innate immune system has undergone a revolution. In particular, it has become clear that all adaptive immune responses are initiated by the innate system, and that recognition of common microbial components by specific receptors is a crucial first step hereby. As many of these components are known to work as adjuvants, this has opened the way to a rational design of novel adjuvants, and the current project aims to take advantage of and contribute to these developments.

The modulation of immune responses -achieved by targeting cell-surface receptors or intracellular pathways- is one of the main goals in the development of new adjuvants. The recently obtained wealth of information about the innate immunity system, including the identification of cognate ligands of innate immunity receptors and the elucidation of downstream signalling pathways, provides a new set of targets for the rational development of novel adjuvants and immunomodulators with well-defined effects on the immune response against specific vaccines. The innate immune system sits at the intersection of the pathways of microbial recognition, inflammation, microbial clearance and cell death. In addition, activation of the innate immune system initiates, amplifies and drives antigen-specific immune responses. To detect the presence of invading microorganisms, it uses receptors that include members of the TLR (Toll-like receptor), NOD (nucleotide-binding oligomerization domain) and CTL (C-type lectin) families.

Aim of the project
This project aims to obtain more knowledge on the role played by innate immunity receptors in the mechanisms by which adjuvants influence the specific immune response to vaccines.

Strategic and innovative aspects
Although many new TLR agonists are currently coming into view, there is still no comprehensive evaluation available of their adjuvant activity with a relevant vaccine antigen, and how this relates to in vitro activation patterns of antigen-presenting cells.

A major focus will be to study the biological activities and adjuvant potential of natural and mutant lipopolysaccharides (LPS) from Neisseria meningitidis and Bordetella pertussis. We have isolated a set of mutants in these bacteria with defects in various steps of the LPS biosynthesis pathway. In particular, mutants with an altered lipid A part of the molecule are altered in their interaction with the innate immunity receptor TLR4, resulting in a reduced inflammatory response. Such LPS derivatives are useful as tools to study the detailed pathways related to adjuvant activity, and have potential as novel non-toxic adjuvants. Interestingly, we have found that some of these mutations also occur naturally among clinical isolates of Neisseria meningitids, where they lead to a less severe form of meningococcal disease.

Planned activities

- Measuring the adjuvant activity of different mutant LPS molecules in mice by immunization with available model antigens for N.meningitidis (meningitis) and B.pertussis (whooping cough) antigens.
- Unraveling the downstream signalling pathways for different LPS mutants. Are the differences only quantitative or also qualitative ?
- Understanding the significance of naturally occurring meningococcal strains with low activation of innate immunity.
- Analyzing the interaction of meningococcal surface components with non-TLR receptors on antigen-presenting cells, such as LPS oligosaccharide with DC-SIGN and Opa proteins with the CEACAM receptors.
- Construction and analysis of Mycobacterium bovis mutants with altered glycolipid and glycoprotein biosynthesis, which may lead to a reduction of its immunosuppressive capabilities.

Planned products

- At least eight scientific publications.
- PhD-thesis.
- Presentation at international conferences.

Foreseen follow-up

Greater mechanistic understanding of innate immunity will allow the design of novel adjuvants tailor-made for specific vaccines and/or routes of immunization, and with a better ratio between effectivity and reactogenicity. Results will be published, and our meningococcal LPS mutants can find application as novel adjuvants. They are already the basis of next-generation outer membrane vesicle vaccines against meningococcal disease being developed by RIVM.

Title:	**Innovative synthetic vaccines: a peptide vaccine against Alzheimer's disease**
Project number:	**S/000102**
Project leader:	Hoogerhout, dhr. dr. ir. P. (Peter) (Cib/VAC/VR)
Start:	01-01-2011
End:	31-12-2011
Total SOR-budget:	€138.717

Motivation

According to the World Alzheimer Report 2009 from Alzheimer's Disease International, 36 million people suffered from Alzheimer's disease. The number of patients is doubling every twenty years. Of the 36 million patients, 28 million

have not received a formal diagnosis. These people have no access to treatment or care.
According to the 2010 Report, the average annual societal costs in high income countries are US$ 32,865 per patient. In the Netherlands, approximately 235,000 people have Alzheimer's disease. The total costs in the Netherlands are estimated to be € 7,5 billion per year (€ 31,900/patient/year).
Vaccination would delay or prevent a progressive neurodegenerative disorder and save considerable sums of money.

Aim of the project
Aim is to anticipate on producing an innovative vaccine against Alzheimer's disease, by an investigation on the preparation of such a vaccine and assessing its immunogenicity in mice. A characteristic of Alzheimer's disease is formation of plaques of protein fibers in the brain. These plaques originate from a membrane-bound protein, the amyloid precursor protein (APP), with a largely unknown biological function. A fragment of 40 or 42 amino acid residues is cleaved enzymatically from the APP, thus forming a peptide called amyloid β (Aβ). Aβ is present in all body fluids and – at first – lacks a defined three-dimensional structure. However, if Aβ reaches a high concentration, it will adopt a hairpin structure and form aggregates. Accumulating studies reveal that soluble small aggregates of Aβ, instead of insoluble Aβ in amyloid plaques, may be the more neurotoxic agent in Alzheimer's disease.
We have targeted an immune response selectively on the turn in the hairpin of misfolded Aβ. Since the response is not targeted on properly folded APP or unfolded Aβ, it will not interfere with the normal physiological processing of APP. In the long term, it may be envisioned that a vaccine with specificity for misfolded amyloid β could be administered prophylactically in the elderly.

Strategic and innovative aspects
There is no current vaccine against Alzheimer's disease. Research on possible vaccination against Alzheimer's disease and other neurodegenerative diseases is relatively new. The present project aims at the rational design of a peptide vaccine against Alzheimer's disease. The peptide will mimic the structure of misfolded Aβ, the neurotoxic agent in Alzheimer's disease.

Planned activities
- Antigen preparation. Familiar protocols will be used for synthesis of a panel of cyclic peptides derived from Aβ. The peptides will be coupled to tetanus toxoid to prepare experimental vaccines.
- Immunization of standard laboratory mice (Balb/c and C57BL/6) to establish the dose and the number of administrations.
- Immunohistology of mouse and human brain tissue with the sera (externally).

Planned products
- 1 Patent.
- 1 Publication.

Foreseen follow-up
At this point, the investigation should be continued by immunization of transgenic model mice for Alzheimer's disease. This requires a grant and experience in the field of neurobiology and immunohistology of brain tissue. It is probably most efficient to formalize collaboration with an external neuroscientific research group to perform this follow-up investigation.

Title:	**Plaform technology for viral vaccines**
Project number:	**S/000105**
Project leader:	Bakker, dhr. dr. ir. W.A.M. (Wilfried) (CIb/VAC/PD)
Start:	01-09-2009
End:	31-12-2013
Total SOR-budget:	€ 2.600.000

Motivation
Public demand for safe and effective vaccines continues to be strong. The greatest hurdle is translating basic science into real vaccines that can be produced according to stringent regulatory requirements. The central issue related to process development is the evolution and translation from a procedure used for making vaccines in a basic research laboratory to a process that can be scaled up and run reproducibly in a large-scale manufacturing environment.

Most vaccines are prophylactic products and difficult to characterize. Therefore, demonstration of product quality and comparability is complicated. As a result, the process = product idea gained acceptance for vaccines. However this "tailor-made" approach presents unacceptable risk because it requires high investments during several years with a low chance of getting beyond phase I/II clinical trials. Also, no knowledge on the biological foundations and no process understanding is being developed in this way. Alternatively, having a science based state-of-the-art platform technology can greatly reduce time, costs and risk because blueprints are available for all documentation and the targeted fast-track process development shows a smooth transfer to process validation studies. Requirement is, of course, that the platform technology is feasible for every (> 90%) of the potential vaccines. Currently, several contract manufacturing companies have adopted such a generic approach successfully for therapeutic protein production processes. However, until now a platform for viral vaccine production is unavailable.

One of the primary goals of a process development program is to increase process productivity, particularly by increasing product titer and purification yields. For many classical vaccines the challenges are to improve process control to meet current guidelines. Further, the required product volume is usually low. Therefore, another challenge is to use more multi-purpose facilities and disposable technology instead of dedicated rooms and hardware. In addition to optimizing product titer and purification yields, a science based process development program should also address: process understanding, operability, scale-ability, robustness, comparability, regulatory risk assessment and economics. For example, the use of disposable and closed process equipment can significantly reduce batch failures and the current validation burden.

Aim of the project
The aim of this study is development and selection of competitive and state-of-the-art platform technologies for specific groups/subclasses of viral vaccines. These platform technologies should provide RIVM with reduced viral vaccine process development time-lines, from approximately 20 years at present to about 10 years.

To improve understanding of the underlying biological principles, various techniques will be applied to elucidate properties of the chosen cell-lines and

their interaction with various viruses. In this way genes and proteins of relevance for adherent and single cell suspension growth, virus entry, and replication will be identified. Using this info, knockdown- or over-expression cell-lines can be generated, which can be used as future hosts for virus culture.

Strategic and innovative aspects
The use of platform technology is an integrated approach with respect to current guidelines which should reduce development timelines for vaccines from 15-20 years at present to 10-12 years as for other biopharmaceuticals.

Such a science-based approach, using Design-of-Experiments methods for optimization studies, has been suggested by the FDA to be the "desired state" for pharmaceutical manufacturing in the 21st century. In this way, knowledge on process development at RIVM will remain state-of-the-art and in pace with demanding regulatory requirements.

Planned activities
- Screening of cell lines to determine their properties and their interaction with various viruses.
- Study of interaction of viruses with the designated cell lines: adaptation, rate limiting steps, effects of adaptation on rate limiting steps.
- Application of 'omics' tools, to elucidate mechanisms.
- Characterization of available disposable bioreactor systems and comparison with standard vessels.
- Development of cell culture strategies for selected cell lines to obtain high cell density culture.
- Define the selection criteria for virus production.
- Development of purification strategies.

Planned products
- Approximately 8 scientific papers.
- One PhD-thesis.
- Approximately 2 lectures at international scientific conferences.
- Approximately 4 posters at international scientific conferences.

Foreseen follow-up
The outlined approach is science-based, and has been suggested by the FDA to be the "desired state" for pharmaceutical manufacturing in the 21st century. In this way, expertise and knowledge of process development at RIVM will remain state-of-the-art, in accordance with demanding regulatory requirements.

A spin-off has been the co-organization of two scientific meetings on collaborative European viral vaccine process development. Also, collaboration with several foreign (and national) universities, institutes, and companies has been initiated.

Based on the current activities and the gained knowlegdge, in combination with additional work in other projects, new assignments by international organizations (e.g. WHO, BMGF, vaccine manufacturers) are anticipated.

Title:	**Immunoproteomics**
Project number:	**S/000191**
Project leader:	Jong, dhr. dr. ir. A.P.J.M. de (Ad) (CIb/VAC/FAR)
Start:	01-06-2009
End:	31-12-2013
Total SOR-budget:	€ 1,980,626

Motivation

Progress in understanding of the protective working mechanisms of vaccines has been hampered by the lack of detailed knowledge on their targets.Various classes of complex vaccines deliver a wide range of foreign antigens to the host. However the specific immune response only targets certain antigens, and within antigens only certain immunogenic epitopes. Immunogenicity of epitopes depends on it's sequence nature, but also on whether an epitope is accessible to and being recognized by one of either class of specific host immune cells, B and T lymphocytes.

There are basic differences between epitopes recognizd by B or T cells. Epitopes recognized by specific B cell receptors, and also by immunoglobulins, their secreted versions in the serum, are parts of intact antigens, with native three-dimensional structure. T cell epitopes on the other hand are typically fragments liberated from intact antigens through proteolytic mechanisms inside host cells.These intracellular epitopes become transported to the cell surface, after binding to chaperone-like molecules known as major histocompatibility complex (MHC) molecules.

Which antigens and epitopes in a vaccine are being targeted by B or T cell responses cannot be predicted *in silico*, due to the highly complex selection process and internal competition between host immune responses. Knowledge on the targets of the protective immune response to vaccines, however, is important in vaccine development and immunosurveillance. Immunoproteomics are dedicated mass spectrometry based methods that can be used to identify the targets of the immune response. By generating protein content information of complex protein samples, immuno-proteomics can verify the presence, in a relative and absolute sense, of certain antigens in a complex vaccine preparation itself. In addition, immunoproteomics can elucidate the source and sequence of unknown epitopes recognized by B cells or T cells, guided by their interaction with immune receptor or chaperone molecules involved.

Aim of the project

The aim of this project is to improve and implement mass spectrometry-based immunoproteomics strategies to comprehensively identify the targets of immune responses to vaccines. Specific subaims are:

- *to bring the mapping of T and B cell epitopes to a higher level*
- *to improve large scale protein identification of complex vaccines*
- *to develop and implement absolute quantitative proteomics strategiesin vaccine research*

Strategic and innovative aspects

Our laboratory is a frontrunner in the field of the identification of T cell epitopes, due to the unique analytical mass spectrometry-based strategy that we have developed over the last decade, a position illustrated by published identification strategies for viral and bacterial T cell epitopes, in collaboation with different (academic) partners.The establishment of our (inter)national collaborative

network in immunology is partially based on the unique value of our expertise/technology in the elucidation of targets of the immune response. Use of (immuno)proteomics in development and (in procss) quality control of vaccines is innovative.

Planned activities

- *Large scale T cell epitope mining.* In this project we will improve both the sensitivity and dynamic range of our immunoproteomics strategy by one order of magnitude (from femtomole to attomole scale).
- *B-cell epitope identification.* We will study the validity of the use of different chemical agents and proteases in terms of their susceptibility to steric hindrance in protein-protein (antigen-antibody) complex systems. First we will validate the method using known B cell epitopes (e.g. diphteria toxoid), followed by the investigation of antigens with unknown or elusive B cell epitopes.
- *Improved proteomics strategy*. We will apply our recently developed protocol to study and optimize protein expression rates in cultures of *Neisseria meningitidis* (meningococcus) at different time points and experimental conditions.
- *Quantitative Biomolecular Mass Spectrometry*. Initially we will focus on getting hands-on experience with published methods in absolute quantitative proteomics, followed by a model study on the determination of the F- and G-protein content in RSV vaccines. It is well-known that both proteins play an essential role in efficacy of the vaccine. Continuation (go decision) in the second and later years requires an additional investment in a state-of-the-art Triple Stage Quadrupole mass spectrometer.

Planned products

- At least four scientific papers.
- A thesis.
- Improved nano-scale LC separation systems (methods).

Foreseen follow-up

If succesfull, the improved immunoproteomics platform will mean a further anchorage in vaccine development, by contributing to identification of (B and T cell) epitopes important in correlates of protection (vaccine lead phase), as well as to *in process* control of the manufacturing process. Examples of pathogens that we may elucidate elusive protective epitopes from, are *Mycobacterium tuberculosis*, influenza virus, measles virus and *Bordetella pertussis*. Such results could lead to improved immunodiagnostics of protective immunity in vaccinees or in the population, and eventually to improvement of vaccines with an optimized targeted protein composition.

Title:	**Alternative vaccine delivery**
Project number:	**S/000192**
Project leader:	Amorij, dhr. dr. J.P. (Jean-Pierre) (CIb/VAC/PM)
Start:	01-01-2011
End:	31-12-2014
Total SOR-budget:	€ 1.980.000

Motivation

Most vaccines are delivered via syringes and needles. Despite their common use, needles and syringes have several drawbacks such as needle stick injuries and the re-use of needles. This causes the spread of diseases, especially in developing countries. Injections, although safe in the Western world and relatively painless, may cause serious stress, fear and concern in children as well as parents. This may lead to reduced participation in vaccination programs. Therefore, only a limited number of injections per immunization session are allowed.

Combining several vaccines in one formulation is an option to reduce the number of injections. But this is difficult due to physicochemical and immunological interference and expensive clinical trials. Therefore we are seeking for alternative delivery methods which are easy to apply and which are painless. Alternatives that are suitable for mass vaccination without the need of trained personnel are also a clear benefit in case of a pandemic outbreak or bioterrorist attacks. Examples of alternative delivery systems are oral, intranasal, pulmonary, dermal delivery and needle free injections. In this project we focus on the delivery through and within the skin and via mucosal surfaces (intranasal, pulmonary and sublingual/buccal),

Aim of the project

The aim of this project is to develop alternatives for needle injections in order to reduce the number of injections. The alternatives should be safe, painless and easy to use. The antigens of interest are hepatitis B, inactivated polio and influenza.

Strategic and innovative aspects

Academic research partners are not able (and willing) to translate the research to a product (lack of registration, GMP, clinical development knowledge). Big pharma is less interested in radically different immunization practices (intrinsic conservatism). Small biotech and device developers do not have access to 'real live' antigens, animal models and licensing expertise. The project involves mucosal vaccination via the nasal, oral or pulmonary tract. The model antigens currently included in the project are Hepatitis B surface antigen (HBsAg), Inactivated Polio Virus (IPV) and Whole Inactivated Influenza Virus (WIV). To date no needle-free alternative for these vaccines is registered. Here we investigate novel vaccine formulations for mucosal vaccination strategies. This will strengthen RIVM's position on the front of formulation and delivery research.

Planned activities

- TMC containing formulations.
  - Physico- and biochemical characterization of the virus particles before and after coating with TMC.
  - Evaluation of antigen processing *ex vivo.*
  - *In vivo* evaluation of the vaccine formulations

- Oral vaccine formulations.
  - Adjuvant screening for sublingual / buccal vaccination.
  - Lyophilization of antigen with stabilizers.
  - Physico- and biochemical characterization of lyophilized antigen and compressed antigen powder, including storage stability.
  - Physical characterization of the vaccine powders.
  - Production of bilayer tablets.
  - Characterization of the vaccine tablets.
  - *In vivo* evaluation of the vaccine tablets (in rats, mice and rabbits/minipigs).
- Spray(freeze)dried vaccine powders & pulmonary vaccine delivery.
  - Drying of antigen with stabilizers.
  - Physico- and biochemical characterization of dried antigen powder. including storage stability.
  - Physical characterization of the vaccine powders.
  - *In vivo* evaluation of the vaccine powders (in mice or rats).

Planned products
- At least four scientific publications.
- At least two lectures at scientific conferences.
- At least three project milestones.

Foreseen follow-up
Follow up of the results may result in acquisition for grants for GMP qualification of the concepts and ultimately to clinical evaluation. Finally proof of concepts should be used to fascilitate partnerships to drive innovation and get needle-free alternatives in vaccination practice.

Title:	**Immunological programming**
Project number:	**S/000193**
Project leader:	Han, mw. W.G.H. (Wanda) (CIb/VAC/VR)
Start:	01-01-2011
End:	14-08-2015
Total SOR-budget:	€ 2.014.753

Motivation
The ultimate goal of vaccination is to develop long-lived immunological protection against infectious diseases in the population. However some vaccines fail to induce sufficiently long-term immunity, resulting in the re-emergence of the disease despite high vaccine coverage. Clonally expanded T and B cell populations specific for vaccine antigens are the key players in immunological protection against vaccine preventable diseases. The induction of not only the right quantity, but rather quality and longevity of these cell types is the basis of successful vaccination. Specific immune responses develop stepwise through three typically phases, i.e. the expansion phase (immediately following immunization), the contraction phase, and the maintenance (memory) phase. However, there is no single standard final outcome of immune responses: T and B cells can be steered towards various cell fates with different functions and memory properties (immunological programming). In addition, the immune system in elderly is less efficient. Furthermore, pathogen adaptation, also due to vaccination, leads to sub-optimal programming by the current vaccines. Therefore it is important to understand how optimal immunological programming can be achieved for each infectious disease and each age group. Alterations in vaccine composition, dosing or the route of antigen, the amount of inflammatory

signals can 'reprogram' the outcome of one or more of the three phases of the immune response, yield a different number, quality or breadth of 'long-term fate' cells and thus a different overall level of protective immunological memory for the host. This knowledge may generate leads for innovation in vaccines and vaccination strategies. This project will use pertussis as a societal relevant model to investigate immunological programming, generating basic knowledge on durability, flexibility and steer-ability of pathogen specific memory immune responses after vaccination.

Aim of the project
This project aims to provide knowledge on the immunological programming of T- and B-cell responses by current vaccine antigens and adjuvants in the host at various ages, thereby creating novel tools to steer specific immunity in the desired direction and tools for immunomonitoring the outcome.

Strategic and innovative aspects
Most research on immunological programming is done in transgenic models specific for irrelevant antigens. Research on programming of T and B cell immune responses to real life infections or vaccines in wild type hosts, such as *Bordetella pertussis* in wild type mice, is a more realistic and original model. Furthermore, this project provides conceptual thinking about failure (or limitations) in immunological programming, e.g. specific for *Bordetella pertussis*. Last but not least, analysis of in vitro innate steering of naïve B cells by vaccine antigens and adjuvants is new.

Planned activities
- In vivo steering of T cell pertussis-specific immune responses.
- In vitro immunological programming of dendritic cells and B cells by pertussis antigen.
- Identification of molecular signatures correlating with extremely programmed immune responses.

Planned products
- Recommendations for pertussis research models.
- At least 4 peer review publications.
- Thesis.

Foreseen follow-up
Fundamental knowledge on the quality and maintenance of immunological memory after vaccination is still limited. Innovating knowledge is important for translational research on new vaccine concepts or strategies.

Title:	**Q fever vaccine based on heterologous expression of O antigen**
Project number:	**S/000206**
Project leader:	Ley, dhr. dr. P.A. van der (Peter) (CIb/VAC/VR)
Start:	01-01-2010
End:	31-12-2012
Total SOR-budget:	€ 668.868

Motivation
Q fever is a zoonosis with worldwide distribution caused by the bacterium *Coxiella burnetii*. Clinical Q fever in most cases presents itself as a self-limiting

flu-like illness with high fever, headache and myalgia, however in some cases pneumonia occurs which requires hospitalization. In a minority of cases a persistent, latent infection may develop that can reactivate months or years later to cause chronic disease. Chronic Q fever is typically found in already immunocompromised patients and most commonly presents as endocarditis. Another, more common complication of Q fever is a disorder similar to chronic fatigue syndrome, which may result from cytokine dysregulation. Due to the very low infectious dose, stability in the environment, and aerosol route of transmission, *C.burnetii* is considered a potential biological weapon.

Sheep and goats are major reservoirs of *C.burnetii*, and the bacteria can be found particularly in their placenta and birth fluids. Humans are most commonly infected through inhalation of contaminated dust or aerosols generated by these animals when held as livestock. In The Netherlands, the number of cases was only 10-20 per year until 2007, when a sharp increase was found in Noord-Brabant, Limburg and Gelderland. This human outbreak was preceded by Q fever causing abortion outbreaks in dairy goat farms in the region and is therefore most likely caused by aerogenic transmission to humans from contaminated farms. Until now, at least 25 patients have died from Q fever infection and many more required hospitalization and/or suffered severe morbidity.

There is no generally available vaccine for Q fever in humans. The only vaccine is not registered for use outside Australia, has limited availability and serious safety drawbacks. The worldwide distribution of Q fever, and its potential as a bioweapon, further underscore the need for novel safe and effective vaccines for general use in humans.

Aim of the project
We will explore the possibility to develop a vaccine against Q fever, based on the known protective O-antigen. By heterologous expression the problems of handling the obligate intracellular BSL-3 pathogen *C.burnetti* will be circumvented, and a safe well-defined acellular vaccine will be the aim of the here proposed feasibility study.

Strategic and innovative aspects
Current efforts for novel Q fever vaccines are limited to improving whole cell vaccines (chloroform/methanol subfraction) and several purified recombinant proteins. Heterologous expression of O antigen is an entirely novel and technically challenging approach for which we are very well positioned given our previous experience and expertise with comparable engineering in *B.pertussis* and *N.meningitidis*.

Planned activities
- Cloning and analysis of the O-antigen locus from the currently circulating Dutch strain.
- Expression of *C.burnetii* O-antigen in *E.coli* and/or *B.pertussis* strains with appropriate low-toxicity lipid A-core structures.
- Immunization of mice with different formulations of the chimeric LPS to measure its immunogenicity and protective capacity.

The final stage will be the testing of the most promising formulations in an animal model of Q fever.

Planned products
By cloning the relevant LPS biosynthesis genes, expression of *C.burnetii* LPS structures in *E.coli* and/or *B.pertussis* will be investigated. If successful, these strains with chimeric LPS will be used for immunization experiments in mice to test for the generation of anti-LPS antibodies.
Results will be published and presented at relevant national and international meetings.

Foreseen follow-up
If successful, the project will give a novel lead for Q fever vaccines which can be further developed with external partners in both the human and veterinary vaccines field. Contacts cq collaborations have already been established with the Central Veterinary Institute and Intervet.

Title:	**Recombinant live attenuated RSV vaccine for the elderly**
Project number:	**S/000207**
Project leader:	Guichelaar, dhr. dr. ir. T. (Teun) (CIb/VAC/VR)
Start:	01-05-2010
End:	30-06-2013
Total SOR-budget:	€ 849.700

Motivation
Respiratory Syncytial Virus (RSV) is the most important causative agent of lower respiratory tract infections in infants, but has also been increasingly recognized as a significant cause of hospitalization, morbidity and mortality in the elderly, with an impact approaching that of non-pandemic influenza virus. Although the disease burden due to these pathogens has not been accurately quantified in developing countries, extrapolation from known figures in industrialized countries, such as 125,000 reported cases of RSV per year in the USA led the World Health Organization to the impressive estimation that RSV causes 64 million infections and 160,000 deaths annually worldwide. Elderly contributed roughly to one-third of these RSV-related hospitalizations. Viral surveillance in the Netherlands indicated that RSV-seasons were associated with excess mortality and hospitalization among the elderly.

A vaccine for the elderly and high-risk adults with underlying cardiopulmonary disease may offer benefits for these persons. The goal of such an RSV vaccine is to prevent lower respiratory tract illness and hospitalizations and deaths associated with RSV infection, by (annual) immunization of elderly. However, there is currently no licensed vaccine against RSV available. An important obstruction for developing an RSV vaccine for the elderly is that RSV illness in elderly has not been studied well. Moreover, in the elderly vaccination should overcome pre-existing immunity to RSV and stimulate the senescent immune response.

Aim of the project
The ultimate goal is to develop a recombinant live attenuated RSV vaccine to protect elderly against RSV-related hospitalization and deaths. The objectives of this project are to develop the aged cotton rat model as a representative and useful animal model for studying mechanisms of protection for RSV disease in

the elderly and to generate innovative RSV vaccine candidates that elicit immunological protection against RSV in the elderly.

Strategic and innovative aspects
Recently RIVM has developed a live attenuated RSV vaccine for infants, which is sufficiently immunogenic and attenuated to warrant clinical evaluation. RIVM expertise on RSV vaccine development will be applied to develop an RSV vaccine for the elderly based on live attenuated recombinant viruses.

There is no animal model available for testing (RSV) vaccines for elderly as yet. The approach of live-attenuated RSV vaccines for the elderly with potential enhanced immunogenicity has not been pursued by others and has not been studied in a representative animal model, such as the (aged) cotton rat model. The cotton rat is a sensitive model for a broad range of human pathogens and therefore highly representative for human infection/vaccination. Because tools that allow analysis of cotton rat immunology are limited (compared to e.g. mouse- and human immunology), we need to extend possibilities for immunology research in the cotton rat and develop novel tools to do so. Development of novel tools that enable thorough analysis of humoral (antibodies) and cellular immunology in the cotton rat model will improve our understanding of RSV-specific immune mechanisms in the elderly and will stimulate and reinforce collaborations with other outstanding vaccine- and immunology research groups.
Moreover, the aged cotton rat vaccination/challenge model can be implemented for other pathogens like influenza and measles.

Planned activities

- Immunology of aged cotton rats: Extending previous feasibility study of aged cotton rats as animal model for testing RSV vaccines for elderly and developing tools for assaying cotton rat immunity.
  - Induction of virus neutralizing antibodies: novel methods enabling analysis of affinity maturation of antibodies and mucosal IgA responses against RSV will be assessed.
  - Induction of cell mediated immunity: Assays to measure protective T and B cell responses will be developed.
- RSV mutants: Design of RSV mutants with potentially increased immunogenicity to overcome immune non responsiveness to RSV in the older host.
  - *In vitro* analysis of mutants.
  - *In vivo* analysis (young and/or elderly cotton rats).
- Adjuvantation of live RSV vaccines: Testing of lipopeptides as adjuvants.
  - Testing of adjuvant activity of other adjuvants, e.g. lipopolysaccharide analogues of *Neisseria meningitis* (in collaboration with Peter van der Ley).
  - Lipopeptide-enhanced infection of recombinant RSV in human cell lines or primary cells.
  - *In vivo* analysis (first in young adult cotton rats, if justified also in elderly cotton rats).

Planned products

- Determination of feasability of the cotton rat model as an ageing model.
- Protocols to analyze cellular (i.e. T- and B-cells) immunology in the cotton rat.
- Protocols to analyze humoral (antibodies) immunology in the cotton rat.
- Novel RSV-mutants as vaccine candidates for improved RSV vaccination.
- Adjuvants for improving RSV vaccination.
- We expect to write scientific manuscripts for publication in international peer-reviewd journals on:
  - The ageing cotton rat model.
  - Improved RSV vaccine.
- We expect to present data on conferences (oral or poster) on:
  - The ageing cotton rat model.
  - Improved RSV vaccine.

Foreseen follow-up

- Development of novel tools for studying immunology in the cotton rat will increase the usefulness of this model, and will therefore improve vaccine research at RIVM as well as vaccine research groups outside RIVM (national and international).
- 'Healthy ageing' is becoming a prominent area of interest due to ageing of the population. Novel insights generated from the aged cotton rat model and development of improved vaccines for the elderly will help solving relevant problems with infectious diseases emerging from the ageing population in the near future.
- Expertise with novel RSV-vaccine candidates (mutants, adjuvantation) will aid improving vaccination strategies for RSV.
- Expertise with the ageing cotton rat model may be useful for finding solutions for other infectious diseases that cause major health problems in the elderly, such as influenza.

Title:	**Vaccinomics: systems biology and vaccinology, molecular signatures of pertussis vaccination**
Project number:	**S/000220**
Project leader:	Metz, dhr. dr. B. (Bernard) (CIb/VAC/FAR
Start:	01-01-2011
End:	31-08-2015
Total SOR-budget:	€ 1.423.400

Motivation
The complexity of the immune system presents a large barrier to understand how protection is generated against many infectious diseases. Lack of knowledge hampers the development of effective vaccines as is illustrated by our inability to develop protective vaccines against HIV, hepatitis C virus, cytomegalovirus, malaria and tuberlosis. Even vaccine-enhanced diseases were shown after vaccination with formaldehyde-inactivated RSV. These and other vaccines need to induce an immune response that goes beyond the induction of antibodies.

Despite great progress in measuring specific parameters of an immune response with sensitivity and precision, vaccine development asks for a more integrated approach to study the mechanisms that form and sustain highly protective immune response. Such an approach is also called 'Systems Biology' that focuses on complex interactions in biological systems, e.g. the entire immune system. Systems biology utilizes, visualizes and explains complex data obtained from multiple experimental sources using typical technology platforms, such as genomics, transcriptomics, proteomics, interactomes etc. The field of systems biology is still in strong development focusing on the development of new experimental technologies and methods for data handling. Many problems have still to be solved in this approach, e.g. the extraction of meaningful data. In spite of these difficulties, the platform becomes an indispensable tool for the development of new vaccines. Systems biology will be involved in studying correlates of protection and administration routes, in developing animal models, vaccine formulations and adjuvants. Systems biology approach can also predict the immunogenicity of vaccines in humans as it has been demonstrated for the yellow fever vaccine.

Aim of the project
The main purpose of this project is to apply systems biology as an integrated approach to assess the effectiveness of vaccines.

Strategic and innovative aspects
System biology is a holistic approach to study complex interactions in biological systems in unbiased manner. In this project we would apply this approach to investigate vaccine-induced responses in animal models and humans. The approach has been utilized to a limited extend for vaccines (see bibliography), and not at all for pertussis vaccines.

Innovative aspects are
- Identification of new genes (or networks) involved in protecting response to *B. pertussis*.
- The application of a sensitive methods to characterize the antibody profile.
- The development functional PCR array to in innate and adaptive immune responses in rats.

Planned activities

- Animal studies with pertussis vaccines: Different types of pertussis vaccines will be used to develop system-based technology for vaccine research.
- Development of functional PCR array: Several blood samples from immunised mice or rats will be analysed in a PCR array. (The PCR array for studying innate and adaptive immunogenicity in rats has to be developed completely) The results of the array will be compared with the functional tests. Also data obtained form different pertussis vaccines will be compared.
- Gene expression profiles: testing in whole genome arrays.
- Immunoproteomics with complex vaccines: the major antigen binding proteins will be identified using 2D electrophoresis, western blotting using antisera and mass spectrometry for antigen identification.
- Assessment of challenge model: Pertussis-vaccinated and non-vaccinated rats (CRM) will be challenged with *B. pertussis* to identify the genetic signatures of a protective immune response.
- Expression profiles of vaccinees: The purpose of this work package is to generate gene-expression profiles from of select number of volunteers that received a booster vaccination with a pertussis vaccine. After the analyses, data will be compared with data from the animal studies.

Planned products

- At least four peer reviewed publications.
- A thesis.

Foreseen follow-up

The approach and technology used in this project will become an indispensable tool for the development and examination of (new) vaccines. It is expected that technology and procedures will be applied in other projects, e.g. for the development and assessment of vaccine formulations, administration routes, correlates of protection and animal models. In particular, the current project will gain detailed insight in the action of the immune system upon pertussis vaccination.

Appendix Project list

Strategic theme Application of new technologies (ANT)

Number	Title	Project leader	Int.
S/210126	Participating in health care IT	Kit Buurman	
S/210136	Using pathogens sequence databases to interpret outbreaks and monitor the National Vaccination Programme	Marijn van Ballegooijen	
S/270186	Impact of medical technology	Johan Polder	
S/340003	Human stem cell technologies	Aldert Piersma	
S/340004	Application of proteomics-based screening assays	Annemieke de Vries	
S/680020	Monitoring networks of the future	Hester Volten	
S/680025	Modeling of elemental carbon and ultra-fine particles	Eric van der Swaluw	*

Int. = international project cofinanced by SOR-budget

Strategic theme Filling the gap: from knowledge to action (FKA)

Number	Title	Project leader	Int.
S/205006	ePublic health: fresh approaches to infectious disease control	Desireé Beaujean	
V/205124/01	Communication with vaccine resistant groups in outbreak situations	Jim van Steenbergen	*
S/210086	Monitoring acceptance national immunisation programme	Hester de Melker	
S/260206	Health literacy put into practice	Ellen Uiters	
S/260216	Factors influencing willingness to participate in preventive interventions: discrete choice experiments	Ardine de Wit	
S/260286	Combining resources in health care: How can we prepare our human resources to exploit our technological resources?	Mattijs Lambooij	
S/270196	Evidence to inform policymaking in public health	Matthijs van den Berg	
S/270206	Improving knowledge utilization	Hans van Oers	
S/270246	CBIs childhood obesity	Marieke Verschuuren	*

Int. = international project cofinanced by SOR-budget

Strategic theme Healthy ageing (HEA)

Number	Title	Project leader	
S/210216	Willingness of elderly to vaccinate	Hester de Melker	
S/260226	Life course approach to ageing	Susan Picavet	
S/260236	Healthy vascular ageing (The impact of lifestyle on diabetes, cardiovascular and kidney diseases and cognitive decline: a life course approach)	Monique Verschuren	
S/260306	Early origins of disease	Alet Wijga	
S/270216	Determinants of social participation in old age	Petra Eysink	
S/340005	Monitoring human ageing	Martijn Dollé	
S/340006	Are supplements good for healthy ageing?	Eugene Jansen	
S/340007	Fetal origin of adult disease	Leo van der Ven	
E/340032	Cofinancing for CHANCES	Euhene Jansen	*
E/340100/01/SO	DNA repair, mutations and cellular aging	Martijn Dollé	*
S/350050	Biomarker associated dietary patterns for improving health of the elderly?	Jolanda Boer	
S/370002	Adequate medication use by elderly outpatients	Diana van Riet - Nales	

Int. = international project cofinanced by SOR-budget

Strategic theme Healthy and sustainable living environments (HSL)

Number	Title	Project leader	Int.
S/260246	Context of health disparities	Annemarie Ruijsbroek	
S/330126	Human entero- (EV)and parechoviruses (HPeV) in water	Saskia Rutjes	
S/607020	Measurably sustainable	Leo Posthuma	
S/607021	Climate cascades (Impact of toxic substances and pathogens on man and ecosystems)	Ton de Nijs	
S/607022	Quantification of ecosystem services for environmental assessment and planning (QESAP)	Michiel Rutgers	
S/680021	Light pollution and the absence of darkness - LightPAD	Dorien Lolkema	
S/680022	Toward as sustainable acoustical environment (TASTE)	Jan Jabben	

Int. = international project cofinanced by SOR-budget

Strategic theme Infectious disease dynamics (IDD)

Number	Title	Project leader	Int.
S/210096	Unveiling the infection dynamics of influenza A	Michiel van Boven	
S/210146	Cytomegalievirus (CMV) infections: disease burden and implications for primary and secondary preventive measures	Hester de Melker	
S/210206	Environmental risk factors for Q fever	Wim van der Hoek	
V/210734/01	EU hepscreen	Susan Hahné	*
S/230176	Assessing population exposure and immunity to new pandemic norovirus strains	Marion Koopmans	
S/230186	Biomarkers for long-term sequels of Q fever	Daan Notermans	
S/230196	Proteomic profiling of XDR TB	Michel Klein	
S/230206	Antivirals against Enteroviruses	Harrie van der Avoort	*
S/230456	Vaccination and pathogen escape (vascape)	Frits Mooi	
S/330136	Control of tick-borne diseases: shooting the messenger	Hein Sprong	
S/330156	ESBL-genes on fresh produce	Hetty Blaak	
V/330524/01/BT	Biotracer, extension 2011	Annemarie Pielaat	*
V/330664/01	SUSCLEAN	Eelco Franz	*

Int. = international project cofinanced by SOR-budget

Strategic theme New dimensions in integrated (risk) assessments in public health and environment (IRA)

Number	Title	Project leader	Int.
S/260256	Impacts of active transport in urban environments (AVENUE)	Wanda Wendel-Vos	
S/260266	Health equity impact	Mariël Droomers	
S/260276	Risk stratification in screening	Annemieke Spijkerman	
S/270226	Dutch DALYs 2.0	Coen van Gool	
S/270236	Towards an eco-epidemiology?	Johan Melse	
S/320003	Towards integration of quantitative toxicogenomics in human toxicological risk assessment (DR-omics)	Wim Mennes	
S/330146	Integration of quantitative microbiological risk assessment and epidemiology (QMRA)	Eric Evers	
S/340008	Assuring saftey without animal testing (ASAT) for respiratory sensitization	Henk van Loveren	

S/601002	Synthetic Biology, Risk benefit evaluations in R&D and product application	Rik Bleijs	
S/607023	Integrated risk assessment nanomaterials (IRAN)	Willie Peijnenburg	
S/607024	Exploration of the nature, extent and policy relevance of potential ecological effects of radio frequency electromagnetic fields (PEER)	Willie Peijnenburg	
S/610004	SCARIER?	Harmen Bijwaard	
S/610020	D-Light&Food	Harry Slaper	
S/610020	D-Light and Food pre	Harry Slaper	
S/610021	Irradiance	Harmen Bijwaard	
E/630017	ENPRA	Ilse Gosens	*
S/630021	Oxidative potential exposure and risk assessment (OPERA)	Nicole Janssen	
S/630022	Healthy action	Hanneke Kruize	
S/630023	Investigating the role of individual attitudes in deciding about uncertain risks: a methodology (IRIDIUM)	Anne Knol	
S/630024	Characterization of idiopathic environmental intolerances (Chi2)	Irene van Kamp	
S/660021	Knowledge integration by physiologically based pharmacokinetic (PBPK) modeling	Claudine Hunault	

Int. = international project cofinanced by SOR-budget

Strategic Vaccine Reasearch (SVR)

Number	**Title**	**Project leader**	**Int.**
S/000083	Innate immunity receptors	Peter van der Ley	
S/000102	Innovative synthetic vaccines: a peptide vaccine against Alzheimer's disease	Peter Hoogerhout	
S/000105	Plaform technology for viral vaccines	Wolfried Bakker	
S/000191	Immunoproteomics	Ad de Jong	
S/000192	Alternative vaccine delivery	Pierre Amorij	
S/000193	Immunological programming	Wanda Han	
S/000206	Q fever vaccine based on heterologous expression of O antigen	Peter van der Ley	
S/000207	Recombinant live attenuated RSV vaccine for the elderly	Teun Guichelaar	
S/000220	Vaccinomics: systems biology and vaccinology, molecular signatures of pertussis vaccination	Bernard Metz	

Int. = international project cofinanced by SOR-budget