Strategic Research RIVM 2011-2014
Project summaries

RIVM Report 000201101
Colophon

© RIVM 2011
Parts of this publication may be reproduced, provided acknowledgement is given to the 'National Institute for Public Health and the Environment', along with the title and year of publication.

J.M.H. Demon (Coordinator Strategic Affairs), RIVM

Contact:
J.M.H. Demon
RIVM
annemiek.demon@rivm.nl

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 six strategic research themes, which together cover 54 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 54 nieuwe projecten, verdeeld over zes speerpunten.

Trefwoorden:
strategisch onderzoek, innovatie, speerpunten, wetenschappelijk
## Contents

1. **Introduction**—9

2. **Application of new technologies (ANT)**—11
   - 2.1 Strategic aims—11
   - 2.2 List ANT—13
   - 2.3 Summaries—14

3. **Filling the gap: from knowledge to action (FKA)**—27
   - 3.1 Strategic aims—27
   - 3.2 List FKA—29
   - 3.3 Summaries—30

4. **Healthy ageing (HEA)**—45
   - 4.1 Strategic aims—45
   - 4.2 List HEA—47
   - 4.3 Summaries—48

5. **Healthy and sustainable living environments (HSL)**—67
   - 5.1 Strategic aims—67
   - 5.2 List HSL—69
   - 5.3 Summaries—70

6. **Infectious disease dynamics (IDD)**—87
   - 6.1 Strategic aims—87
   - 6.2 List IDD—89
   - 6.3 Summaries—90

7. **New dimensions in integrated (risk) assessments in public health and environment (IRA)**—109
   - 7.1 Strategic aims—109
   - 7.2 List IRA—111
   - 7.3 Summaries—112

Appendix Project list—149
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 are selected for the period 2011-2014. The selection of the projects was completed in November 2011.

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, six 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).

The next six chapters comprise a description of the six 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 value
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.

Outline and scope in relation to RIVM’s mission
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.

Focal points and project guidelines
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.

Opportunities for international cooperation
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

<table>
<thead>
<tr>
<th>Number</th>
<th>Title</th>
<th>Project leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>S/210126</td>
<td>Participating in health care IT</td>
<td>Kit Buurman</td>
</tr>
<tr>
<td>S/210136</td>
<td>Using pathogens sequence databases to interpret outbreaks and monitor the National Vaccination programme</td>
<td>Marijn van Ballegooijen</td>
</tr>
<tr>
<td>S/270186</td>
<td>Impact of medical technology</td>
<td>Johan Polder</td>
</tr>
<tr>
<td>S/340003</td>
<td>Human stem cell technologies</td>
<td>Aldert Piersma</td>
</tr>
<tr>
<td>S/340004</td>
<td>Application of proteomics-based screening assays</td>
<td>Annemieke de Vries</td>
</tr>
<tr>
<td>S/680020</td>
<td>Monitoring networks of the future</td>
<td>Hester Volten</td>
</tr>
</tbody>
</table>
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.
**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:
  o 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.
  o 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.
  o 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.

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

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

3.1 Strategic aims

Societal value
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. Of 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.

Outline and scope in relation to RIVM’s mission
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.

Focal points and project guidelines
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.

**Opportunities for international cooperation**

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
<table>
<thead>
<tr>
<th>Number</th>
<th>Title</th>
<th>Project leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>S205006</td>
<td>ePublic health: fresh approaches to infectious disease control</td>
<td>Desireé Beaujean</td>
</tr>
<tr>
<td>S210086</td>
<td>Monitoring acceptance national immunization programme</td>
<td>Hester de Melker</td>
</tr>
<tr>
<td>S260206</td>
<td>Health literacy put into practice</td>
<td>Ellen Uiters</td>
</tr>
<tr>
<td>S260216</td>
<td>Factors influencing willingness to participate in preventive interventions: discrete choice experiments</td>
<td>Ardine de Wit</td>
</tr>
<tr>
<td>S260286</td>
<td>Combining resources in health care: How can we prepare our human resources to exploit our technological resources?</td>
<td>Mattijs Lambooij</td>
</tr>
<tr>
<td>S270196</td>
<td>Evidence to inform policymaking in public health</td>
<td>Matthijs van den Berg</td>
</tr>
<tr>
<td>S270206</td>
<td>Improving knowledge utilization</td>
<td>Hans van Oers</td>
</tr>
</tbody>
</table>
3.3 Summaries

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

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.e. disease control and prevention in the 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: 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 criticize, 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/conversations 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.
Factors influencing willingness to participate in preventive interventions: discrete choice experiments

S/260216
Dr. G.A. de Wit (Ardine) (V&Z-PZO)
01-01-2011
31-12-2014
€ 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 costs: € 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 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 adds 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

<table>
<thead>
<tr>
<th>Project number:</th>
<th>S/270196</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project leader:</td>
<td>Dr. M. van den Berg (Matthijs) (V&amp;Z/VTW)</td>
</tr>
<tr>
<td>Start:</td>
<td>01-01-2011</td>
</tr>
<tr>
<td>End:</td>
<td>31-12-2013</td>
</tr>
<tr>
<td>Total SOR-budget:</td>
<td>€ 313,600</td>
</tr>
</tbody>
</table>

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 and 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, resources 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.

<table>
<thead>
<tr>
<th>Title:</th>
<th>Improving knowledge utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project number:</td>
<td>S/270206</td>
</tr>
<tr>
<td>Project leader:</td>
<td>Prof. dr. ing. J.A.M. van Oers (Hans) (V&amp;Z/VTV)</td>
</tr>
<tr>
<td>Start:</td>
<td>01-01-2011</td>
</tr>
<tr>
<td>End:</td>
<td>31-12-2014</td>
</tr>
<tr>
<td>Total SOR-budget:</td>
<td>€ 474,800</td>
</tr>
</tbody>
</table>

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.
4 Healthy ageing (HEA)

4.1 Strategic aims

Societal value
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.

Outline and scope in relation to RIVM’s mission
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.

Focal points and project guidelines
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.

Opportunities for international cooperation
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

<table>
<thead>
<tr>
<th>Number</th>
<th>Title</th>
<th>Project leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>S210216</td>
<td>Willingness of elderly to vaccinate</td>
<td>Hester de Melker</td>
</tr>
<tr>
<td>S260226</td>
<td>Life course approach to ageing</td>
<td>Susan Picavet</td>
</tr>
<tr>
<td>S260236</td>
<td>Healthy vascular ageing (The impact of lifestyle on diabetes, cardiovascular and kidney diseases and cognitive decline: a life course approach)</td>
<td>Monique Verschuren</td>
</tr>
<tr>
<td>S270216</td>
<td>Determinants of social participation in old age</td>
<td>Petra Eysink</td>
</tr>
<tr>
<td>S340005</td>
<td>Monitoring human ageing</td>
<td>Martijn Dollé</td>
</tr>
<tr>
<td>S340006</td>
<td>Are supplements good for healthy ageing?</td>
<td>Eugene Jansen</td>
</tr>
<tr>
<td>S340007</td>
<td>Fetal origin of adult disease</td>
<td>Leo van der Ven</td>
</tr>
<tr>
<td>S370002</td>
<td>Adequate medication use by elderly outpatients</td>
<td>Diana Riet-van Nales</td>
</tr>
</tbody>
</table>
4.3 Summaries

Title: Willingness of elderly to vaccinate
Project number: S/210216
Project leader: Dr. H.E. de Melker (Hester) (Clb-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 lifestyle around the age of 20 crucial for healthy ageing? How many persons change their lifestyle 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 lifestyle 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 lifestyle 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 lifestyle.
- Explore how changes in lifestyle 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 lifestyle 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.
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:** 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, lifestyle 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, lifestyle, 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 interconventions 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) in 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.
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 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 safe 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 fulfill 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: Adequate medication use by elderly outpatients
Project number: S/370002
Project leader: Drs. D.A. Riet-van 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-manage 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 rupturable 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 advise 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.
Healthy and sustainable living environments (HSL)

5.1 Strategic aims

Societal value
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.

Outline and scope in relation to RIVM’s mission
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.

Focal points and project guidelines
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).
Opportunities for international cooperation
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, CO₂-balancing
### 5.2 List HSL

<table>
<thead>
<tr>
<th>Number</th>
<th>Title</th>
<th>Project leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>S260246</td>
<td>Context of health disparities</td>
<td>Annemarie Ruijsbroek</td>
</tr>
<tr>
<td>S330126</td>
<td>Human entero- (EV) and parechoviruses (HPeV) in water</td>
<td>Saskia Rutjes</td>
</tr>
<tr>
<td>S607020</td>
<td>Measurably sustainable</td>
<td>Leo Posthuma</td>
</tr>
<tr>
<td>S607021</td>
<td>Climate cascades (Impact of toxic substances and pathogens on man and ecosystems)</td>
<td>Ton de Nijs</td>
</tr>
<tr>
<td>S607022</td>
<td>Quantification of ecosystem services for environmental assessment and planning (QESAP)</td>
<td>Michiel Rutgers</td>
</tr>
<tr>
<td>S680021</td>
<td>Light pollution and the absence of darkness - LightPAD</td>
<td>Dorien Lolkema</td>
</tr>
<tr>
<td>S680022</td>
<td>Toward a sustainable acoustical environment (TASTE)</td>
<td>Jan Jabben</td>
</tr>
</tbody>
</table>
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.

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.

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

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 to 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.
- 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.

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

**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.
**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 try to formulate an exposure effect relation between artificial night time light and annoyance.
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 soundscape 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_{Aeq} 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 value
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.

Outline and scope in relation to RIVM’s mission
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.

Focal points and project guidelines
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.

Opportunities for international cooperation
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

<table>
<thead>
<tr>
<th>Number</th>
<th>Title</th>
<th>Project leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>S210096</td>
<td>Unveiling the infection dynamics of influenza A</td>
<td>Michiel van Boven</td>
</tr>
<tr>
<td>S210146</td>
<td>Cytomegalovirus (CMV) infections: disease burden and implications for primary and secondary preventive measures</td>
<td>Hester de Melker</td>
</tr>
<tr>
<td>S210206</td>
<td>Environmental risk factors for Q fever</td>
<td>Wim van der Hoek</td>
</tr>
<tr>
<td>S230176</td>
<td>Assessing population exposure and immunity to new pandemic norovirus strains</td>
<td>Marion Koopmans</td>
</tr>
<tr>
<td>S230186</td>
<td>Biomarkers for long-term sequels of Q fever</td>
<td>Daan Notermans</td>
</tr>
<tr>
<td>S230196</td>
<td>Proteomic Profiling of XDR TB</td>
<td>Michel Klein</td>
</tr>
<tr>
<td>S230456</td>
<td>Vaccination and pathogen escape (vacscape)</td>
<td>Frits Mooi</td>
</tr>
<tr>
<td>S330136</td>
<td>Control of tick-borne diseases: shooting the messenger</td>
<td>Hein Sprong</td>
</tr>
<tr>
<td>S330156</td>
<td>ESBL genes on fresh produce</td>
<td>Hetty Blaak</td>
</tr>
</tbody>
</table>
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 costs:** € 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 costs: € 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) (Clb–EPI)
Start: 01-01-2011
End: 31-12-2014
Total costs: € 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.
**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 serum bank 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.
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 \textit{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 costs:** € 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) \textit{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) antimicrobial 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:** 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 costs:** € 527,456

**Motivation**

Widespread vaccination of children was successful in significantly reducing pertussis morbidity and mortality. However, despite vaccination, *Bordetella 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.
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 costs: € 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 a 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.
New dimensions in integrated (risk) assessments in public health and environment (IRA)

7.1 Strategic aims

Societal value
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.

Outline and scope in relation to RIVM’s mission
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.

Focal points and project guidelines
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.

Opportunities for international cooperation
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
### List IRA

<table>
<thead>
<tr>
<th>Number</th>
<th>Title</th>
<th>Project leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>S260256</td>
<td>Impacts of active transport in urban environments (AVENUE)</td>
<td>Wanda Wendel-Vos</td>
</tr>
<tr>
<td>S260266</td>
<td>Health equity impact</td>
<td>Mariël Droomers</td>
</tr>
<tr>
<td>S260276</td>
<td>Risk stratification in screening</td>
<td>Annemieke Spijkerman</td>
</tr>
<tr>
<td>S270226</td>
<td>Dutch DALYs 2.0</td>
<td>Coen van Gool</td>
</tr>
<tr>
<td>S270236</td>
<td>Towards an eco-epidemiology?</td>
<td>Johan Melse</td>
</tr>
<tr>
<td>S320003</td>
<td>Towards integration of quantitative toxicogenomics in human toxicological risk assessment (DR-omics)</td>
<td>Wim Mennes</td>
</tr>
<tr>
<td>S330146</td>
<td>Integration of quantitative microbiological risk assessment and epidemiology (QMRA)</td>
<td>Eric Evers</td>
</tr>
<tr>
<td>S340008</td>
<td>Assuring safety without animal testing (ASAT) for respiratory sensitization</td>
<td>Henk van Loveren</td>
</tr>
<tr>
<td>S607023</td>
<td>Integrated risk assessment nanomaterials (IRAN)</td>
<td>Willie Peijnenburg</td>
</tr>
<tr>
<td>S607024</td>
<td>Exploration of the nature, extent and policy relevance of potential ecological effects of radio frequency electromagnetic fields (PEER)</td>
<td>Willie Peijnenburg</td>
</tr>
<tr>
<td>S610020</td>
<td>D-light and food pre</td>
<td>Harry Slaper</td>
</tr>
<tr>
<td>S610021</td>
<td>Irradiance</td>
<td>Harmen Bijwaard</td>
</tr>
<tr>
<td>S630021</td>
<td>Oxidative potential exposure and risk assessment (OPERA)</td>
<td>Nicole Janssen</td>
</tr>
<tr>
<td>S630022</td>
<td>Healthy action</td>
<td>Hanneke Kruize</td>
</tr>
<tr>
<td>S630023</td>
<td>Investigating the role of individual attitudes in deciding about uncertain risks: a methodology (IRIDIUM)</td>
<td>Anne Knol</td>
</tr>
<tr>
<td>S630024</td>
<td>Characterization of idiopathic environmental intolerances (Chi2)</td>
<td>Irene van Kamp</td>
</tr>
<tr>
<td>S660021</td>
<td>Knowledge integration by physiologically based pharmacokinetic (PBPK) modelling</td>
<td>Claudine Hunault</td>
</tr>
</tbody>
</table>
7.3 Summaries

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

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.

**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.
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 HEAfs 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 and 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 to 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.
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 the Netherlands 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 animal 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).

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

**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 m³). 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 TiO₂, CeO₂ 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.
• 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.

<table>
<thead>
<tr>
<th align="right">Title:</th>
<th>Exploration of the nature, extent and policy relevance of potential ecological effects of radio frequency electromagnetic fields (PEER)</th>
</tr>
</thead>
<tbody>
<tr>
<td align="right">Project number:</td>
<td>S/607024</td>
</tr>
<tr>
<td align="right">Project leader:</td>
<td>Prof. dr. ir. W.J.G.M. Peijnenburg (Willie) (MEV-LER)</td>
</tr>
<tr>
<td align="right">Start:</td>
<td>01-03-2011</td>
</tr>
<tr>
<td align="right">End:</td>
<td>29-02-2012</td>
</tr>
<tr>
<td align="right">Total SOR-budget:</td>
<td>€ 92,565</td>
</tr>
</tbody>
</table>

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

**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: 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.

<table>
<thead>
<tr>
<th>Title:</th>
<th>Irradiance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project number:</td>
<td>S/610021</td>
</tr>
<tr>
<td>Project leader:</td>
<td>Dr. H. Bijwaard (Harmen) (MEV-LSO)</td>
</tr>
<tr>
<td>Start:</td>
<td>01-01-2011</td>
</tr>
<tr>
<td>End:</td>
<td>31-12-2013</td>
</tr>
<tr>
<td>Total SOR-budget:</td>
<td>€ 200,000</td>
</tr>
</tbody>
</table>

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 authoritative 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.

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

**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 (IRIDIUIM)

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.
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 intoxitations) 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.
## Appendix Project list

### Strategic theme Application of new technologies (ANT)

<table>
<thead>
<tr>
<th>Number</th>
<th>Title</th>
<th>Project leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>S210126</td>
<td>Participating in health care IT</td>
<td>Kit Buurman</td>
</tr>
<tr>
<td>S210136</td>
<td>Using pathogens sequence databases to interpret outbreaks and monitor the National Vaccination Programme</td>
<td>Marijn van Ballegooijen</td>
</tr>
<tr>
<td>S270186</td>
<td>Impact of medical technology</td>
<td>Johan Polder</td>
</tr>
<tr>
<td>S340003</td>
<td>Human stem cell technologies</td>
<td>Aldert Piersma</td>
</tr>
<tr>
<td>S340004</td>
<td>Application of proteomics-based screening assays</td>
<td>Annemieke de Vries</td>
</tr>
<tr>
<td>S680020</td>
<td>Monitoring networks of the future</td>
<td>Hester Volten</td>
</tr>
</tbody>
</table>

### Strategic theme Filling the gap: from knowledge to action (FKA)

<table>
<thead>
<tr>
<th>Number</th>
<th>Title</th>
<th>Project leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>S205006</td>
<td>ePublic health: fresh approaches to infectious disease control</td>
<td>Desireé Beaujean</td>
</tr>
<tr>
<td>S210086</td>
<td>Monitoring acceptance national immunization programme</td>
<td>Hester de Melker</td>
</tr>
<tr>
<td>S260206</td>
<td>Health literacy put into practice</td>
<td>Ellen Uiters</td>
</tr>
<tr>
<td>S260216</td>
<td>Factors influencing willingness to participate in preventive interventions: discrete choice experiments</td>
<td>Ardine de Wit</td>
</tr>
<tr>
<td>S260286</td>
<td>Combining resources in health care: How can we prepare our human resources to exploit our technological resources?</td>
<td>Mattijs Lambooij</td>
</tr>
<tr>
<td>S270196</td>
<td>Evidence to inform policymaking in public health</td>
<td>Matthijs van den Berg</td>
</tr>
<tr>
<td>S270206</td>
<td>Improving knowledge utilization</td>
<td>Hans van Oers</td>
</tr>
</tbody>
</table>

### Strategic theme Healthy ageing (HEA)

<table>
<thead>
<tr>
<th>Number</th>
<th>Title</th>
<th>Project leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>S210216</td>
<td>Willingness of elderly to vaccinate</td>
<td>Hester de Melker</td>
</tr>
<tr>
<td>S260226</td>
<td>Life course approach to ageing</td>
<td>Susan Picavet</td>
</tr>
<tr>
<td>S260236</td>
<td>Healthy vascular ageing (The impact of lifestyle on diabetes, cardiovascular and kidney diseases and cognitive decline: a life course approach)</td>
<td>Monique Verschuren</td>
</tr>
<tr>
<td>S270216</td>
<td>Determinants of social participation in old age</td>
<td>Petra Eysink</td>
</tr>
<tr>
<td>S340005</td>
<td>Monitoring human ageing</td>
<td>Martijn Dollé</td>
</tr>
<tr>
<td>S340006</td>
<td>Are supplements good for healthy ageing?</td>
<td>Eugene Jansen</td>
</tr>
<tr>
<td>S340007</td>
<td>Fetal origin of adult disease</td>
<td>Leo van der Ven</td>
</tr>
<tr>
<td>S370002</td>
<td>Adequate medication use by elderly outpatients</td>
<td>Diana van Riet-van Nales</td>
</tr>
</tbody>
</table>
Strategic theme Healthy and sustainable living environments (HSL)

<table>
<thead>
<tr>
<th>Number</th>
<th>Title</th>
<th>Project leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>S260246</td>
<td>Context of health disparities</td>
<td>Annemarie Ruijsbroek</td>
</tr>
<tr>
<td>S330126</td>
<td>Human entero- (EV)and parechoviruses (HPeV) in water</td>
<td>Saskia Rutjes</td>
</tr>
<tr>
<td>S607020</td>
<td>Measurably sustainable</td>
<td>Leo Posthuma</td>
</tr>
<tr>
<td>S607021</td>
<td>Climate cascades (Impact of toxic substances and pathogens on man and ecosystems)</td>
<td>Ton de Nijs</td>
</tr>
<tr>
<td>S607022</td>
<td>Quantification of ecosystem services for environmental assessment and planning (QESAP)</td>
<td>Michiel Rutgers</td>
</tr>
<tr>
<td>S680021</td>
<td>Light pollution and the absence of darkness - LightPAD</td>
<td>Dorien Lolkema</td>
</tr>
<tr>
<td>S680022</td>
<td>Toward a sustainable acoustical environment (TASTE)</td>
<td>Jan Jabben</td>
</tr>
</tbody>
</table>

Strategic theme Infectious disease dynamics (IDD)

<table>
<thead>
<tr>
<th>Number</th>
<th>Title</th>
<th>Project leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>S210096</td>
<td>Unveiling the infection dynamics of influenza A</td>
<td>Michiel van Boven</td>
</tr>
<tr>
<td>S210146</td>
<td>Cytomegalievirus (CMV) infections: disease burden and implications for primary and secondary preventive measures</td>
<td>Hester de Melker</td>
</tr>
<tr>
<td>S210206</td>
<td>Environmental risk factors for Q fever</td>
<td>Wim van der Hoek</td>
</tr>
<tr>
<td>S230176</td>
<td>Assessing population exposure and immunity to new norovirus strains</td>
<td>Marion Koopmans</td>
</tr>
<tr>
<td>S230186</td>
<td>Biomarkers for long-term sequels of Q fever</td>
<td>Daan Notermans</td>
</tr>
<tr>
<td>S230196</td>
<td>Proteomic Profiling of XDR TB</td>
<td>Michel Klein</td>
</tr>
<tr>
<td>S230456</td>
<td>Vaccination and pathogen escape (vascape)</td>
<td>Frits Mooi</td>
</tr>
<tr>
<td>S330136</td>
<td>Control of tick-borne diseases: shooting the messenger</td>
<td>Hein Sprong</td>
</tr>
<tr>
<td>S330156</td>
<td>ESBL genes on fresh produce</td>
<td>Hetty Blaak</td>
</tr>
</tbody>
</table>
Strategic theme New dimensions in integrated (risk) assessments in public health and environment (IRA)

<table>
<thead>
<tr>
<th>Number</th>
<th>Title</th>
<th>Project leader</th>
</tr>
</thead>
<tbody>
<tr>
<td>S260256</td>
<td>Impacts of active transport in urban environments (AVENUE)</td>
<td>Wanda Wendel-Vos</td>
</tr>
<tr>
<td>S260266</td>
<td>Health equity impact</td>
<td>Mariël Droomers</td>
</tr>
<tr>
<td>S260276</td>
<td>Risk stratification in screening</td>
<td>Annemieke Spijkerman</td>
</tr>
<tr>
<td>S270226</td>
<td>Dutch DALYs 2.0</td>
<td>Coen van Gool</td>
</tr>
<tr>
<td>S270236</td>
<td>Towards an eco-epidemiology?</td>
<td>Johan Melse</td>
</tr>
<tr>
<td>S320003</td>
<td>Towards integration of quantitative toxicogenomics in human toxicological risk assessment (DR-omics)</td>
<td>Wim Mennes</td>
</tr>
<tr>
<td>S330146</td>
<td>Integration of quantitative microbiological risk assessment and epidemiology (QMRA)</td>
<td>Eric Evers</td>
</tr>
<tr>
<td>S340008</td>
<td>Assuring safety without animal testing (ASAT) for respiratory sensitization</td>
<td>Henk van Loveren</td>
</tr>
<tr>
<td>S607023</td>
<td>Integrated risk assessment nanomaterials (IRAN)</td>
<td>Willie Peijnenburg</td>
</tr>
<tr>
<td>S607024</td>
<td>Exploration of the nature, extent and policy relevance of potential ecological effects of radio frequency electromagnetic fields (PEER)</td>
<td>Willie Peijnenburg</td>
</tr>
<tr>
<td>S610020</td>
<td>D-Light and food pre</td>
<td>Harry Slaper</td>
</tr>
<tr>
<td>S610021</td>
<td>Irradiance</td>
<td>Harmen Bijwaard</td>
</tr>
<tr>
<td>S630021</td>
<td>Oxidative potential exposure and risk assessment (OPERA)</td>
<td>Nicole Janssen</td>
</tr>
<tr>
<td>S630022</td>
<td>Healthy action</td>
<td>Hanneke Kruize</td>
</tr>
<tr>
<td>S630023</td>
<td>Investigating the role of individual attitudes in deciding about uncertain risks: a methodology (IRIDIUM)</td>
<td>Anne Knol</td>
</tr>
<tr>
<td>S630024</td>
<td>Characterization of idiopathic environmental intolerances (Chi2)</td>
<td>Irene van Kamp</td>
</tr>
<tr>
<td>S660021</td>
<td>Knowledge integration by physiologically based pharmacokinetic (PBPK) modelling</td>
<td>Claudine Hunault</td>
</tr>
</tbody>
</table>
Strategic Research RIVM 2011-2014
Project summaries

Report 000201101/2011
J.M.H. Demon