Strategic Research RIVM (SOR) 2007-2010
Summaries Project Proposals
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15 December 2006
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</tr>
</tbody>
</table>
Contents

Preface.............................................................................................................................................. 5
1 Risk Assessment, Perception, and Consumer Behaviour and Understanding (RPC) .......... 7
2 Emergency Response Functions and Safety (ERF) ............................................................... 23
3 Infectious Diseases (INF)........................................................................................................... 39
4 Chronic Diseases, Intervention and Lifestyle (CIL) ............................................................. 61
5 Medicines and Functional Foods (MFF) .................................................................................. 99
6 Environmental Quality and Health (EQH) ............................................................................. 107
Preface

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

Aim of the Strategic Research Program

The aim of the Strategic Research Program is to safeguard the scientific continuity of RIVM either by filling knowledge gaps, or by anticipating on new or future developments to reinforce the institute's national and international position.

According to this aim, six strategic themes were formulated:

- Risk Assessment, Perception, and Consumer Behaviour and Understanding
- Emergency Response Functions and Safety
- Infectious Diseases
- Chronic Diseases, Intervention and Lifestyle
- Medicines and Functional Foods
- Environmental Quality and Health

Criteria for selection

The submitted proposals had to fit into one of the strategic themes. The proposals were evaluated based on a number of criteria in order to be eligible for financing through SOR:

Research questions/approach

- The proposal has realistic goals and is clearly formulated
- Transparency on potential critical moments within the project
- Clear description of the expected results
- The project facilitates new national and/or international collaborations

Strategic or innovative nature

- It addresses key tasks of RIVM and fits within one of the six strategic themes
- The project is needed to assure continuity in the field of research/knowledge for RIVM
- The project anticipates on new developments, with a high potential of generating new assignments
- The project contributes to the (inter)national scientific position of RIVM
- The project addresses serious threatening knowledge gaps
In this report
The following chapters each comprise a strategic theme. After a short description of the theme the projects are listed. Each accepted project proposal is summarized. Abbreviations behind the name of the project leader indicate organizational units within RIVM. Total costs are provisional estimated lifetime costs (2007-2010) of the projects. Some projects will continue after this period, these costs are not included.
1 Risk Assessment, Perception, and Consumer Behaviour and Understanding (RPC)

This theme represents a key competence of RIVM, which is important for all research sectors. Working on this theme also implies strong opportunities for intersectional cooperation. Risk assessment, perception & consumer behaviour are relevant research subjects, appropriate for the major RIVM knowledge areas such as source of threat, effect studies, system functions and effective interventions.

Projects

<table>
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<tr>
<th>Project number</th>
<th>Title</th>
<th>Author</th>
<th>Costs (€)</th>
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<tbody>
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<td>S/270136</td>
<td>GettingBetter.nl</td>
<td>Van Loon</td>
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<td>S/260196</td>
<td>Effective use Performance Indicators</td>
<td>Graafmans</td>
<td>216,000</td>
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<tr>
<td>S/340010</td>
<td>Toxicogenomics in Risk Assessment</td>
<td>Van Steeg</td>
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<td>Methods for Dietary Exposure Assessment</td>
<td>Ocké</td>
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<td>S/340050</td>
<td>Alternatives for Animal Testing</td>
<td>Opperhuizen</td>
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Motivation

In the Netherlands several large scale population screening programs are in place, with screening for breast- and cervical cancer, Down’s syndrome during pregnancy and the neonatal ‘heelprick’ as well known examples. In addition to these routinely performed population screening programs, several ad hoc screenings take place in humans for pathogens in case of infectious outbreaks to identify cause of disease. In all these screenings the RIVM plays an important role in coordinating and in some cases executing and/or validating the programs. For both population and ad hoc screenings an increase in the number of screenings as well as the number of individuals to be screened is expected in the near future. This emphasizes the need for further development of new sensitive screening methods with less false positive and negative results. The focus of the current project proposal will be the development of assays for the detection of disease markers in human body fluids based on proteomics techniques.

Aim of the project

The general aim of this project is to set up and implement proteomic techniques to develop new assays for various screening programs at the RIVM. Application of the proteomics technology for large-scale detection of diseases or conditions in the population would allow the RIVM to rapidly and with a high-throughput approach detect and monitor the cause of infections, and will improve and support performing the population screening programs. The specific objectives are:

- Set up and implement proteomic techniques necessary for detection of proteins in human body fluids at the RIVM, and obtain up to date expertise in this field,
- Explore the possibilities to use innovative proteomic techniques for routine population screening programs or specific ad hoc screening applications,
- Develop proteomic assays for pathogen surveillance, Down syndrome screening in early pregnancy and detection of breast cancer in human serum to improve screening, as a ‘proof of principle’ towards high-throughput assays for use in population screenings.

Strategic and innovative aspects

The RIVM plays an important role in routine population screening programs and has a leading role in monitoring infectious outbreaks. It is essential for RIVM to be actively involved in the development of new innovative assays that can be used for these monitoring functions. Proteomics is a technology that is (inter)nationally rapidly progressing and very promising to be used in screenings programs as it allows screening of a set of relevant proteins in body fluids in a fast and high-throughput manner.

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1 This project is related to: V/230024/01/DS Down syndrome screening, V/230024/06/NS neonatal screening, S/340200 (SOR-project Genomics; 2002 - 2006), S/650090/04 (NIEHS project on subject cancer), S/232101/01/AA Biosafety, V/210690/01/SSO control inf. dis., V/600000/01/AE viral diagnostics
Planned activities

The project can be divided in three distinct phases: 1) expanding our knowledge of proteomics, 2) testing of protocols and 3) analysis of an initial series of samples. If these first analyses prove to be successful, the protocols can be further scaled up and streamlined into standardized assays.

The project consists of the following sub-projects:
1. Inventory of (inter)nationally ongoing research and implementation of proteomics techniques at the RIVM.
2. Bioinformatics and statistical analysis.
3. Detection of immunological responses to pathogens.
5. Early detection of Down syndrome fetus through detection of predictive biomarkers in serum of the mother.
6. Detection of specific diseases in the neonatal population-screening program.

Planned products

- Development and implementation of proteomics techniques, methods, and bioinformatics at the RIVM, resulting in several standard techniques and assays applicable to a wide range of screenings in populations for now and new questions and applications in the future.
- "Vital knowledge" concerning proteomics and its usage in population screening programs.
- A platform consisting of proteomics expertise, techniques, and equipment accessible for other proteomics users within the RIVM with research questions.
- Networks with researchers involved in development of proteomics techniques and in applying these techniques for human screening purposes.
- Peer reviewed publications.
- A RIVM report describing the principles and background of proteomics, and the potential uses at the RIVM.
- Workshop familiarizing the RIVM with the proteomics technique and its potentials for RIVM research lines and tasks.

Foreseen follow-up

Results of this project should provide the starting point to actually implement proteomics techniques in routine clinical screening in the years immediately following the end of this project.

Implementation of proteomics techniques at the RIVM will have benefits for a broader field of applications. For example, this system has enormous potential to be used as an epidemiological tool (rapid, sensitive, accurate and adaptable to other infections) to screen human body fluids for many types of clinical syndromes and outbreaks (preparedness). We will create a proteomics platform for other researchers. In addition, in year four of the project an RIVM report will be generated describing the above for a broader RIVM readership.
Title: GettingBetter.nl
Project number: S/270136 (V_Z.18)
Project leader: Dr. Ir. A.J.M. van Loon (VTW)
Start: 01-01-2007
End: 31-12-2010
Total costs: € 512,000

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

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

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

Strategic and innovative aspects
The project evolves from the practical and theoretical need for evidence with regard to key questions in a consumer centred health care system. It aims to work on a new science area within the RIVM in cooperation with external experts. The innovative nature is further implied by the current lack of data in a wide range of e-health related issues. A combined and innovative effort to meet these needs could seriously advance current and future public enterprises. The output will be valuable for the institute’s current projects, particularly for her new public assignments and statutory responsibilities, and will thus attract new investors.

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

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2 The project is related to other public informational assignments of RIVM e.g. the National Vaccination Program. There are relations to nationals projects (e.g. UMC St.Radboud Nijmegen, University of Twente) and international institutes e.g. the Toronto General Research Institute of the UHN (Canada) or the Bertelsmann Stiftung, Gütersloh (Germany).
Planned products

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

Foreseen follow-up

Implementation of results and output will enhance (future) RIVM products/projects aimed at informing citizens on public health, nutrition, safety and the environment. It will contribute to public and professional visibility. It will facilitate acquisition of follow-up investment; endorse its national and international position as demonstrated by presence in / organization of relevant scientific and policy forums. The outcomes serve the public interest and the public interest only.
Title: Effective Use Performance Indicators
Project number: S/260196 (V.Z.30)
Project leader: Dr. W.C. Graafmans (PZO)
Start: 01-01-2007
End: 31-12-2010
Total costs: € 216,000

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

Aim of the project
General aim is to study how health care professionals can use performance/quality indicators to improve the quality of care provided to their patients in the hospital. Specific aims:
- To select sets of quality indicators for hospital care by medical specialists, in the domains of clinical practise, governance, and patient safety.
- To explore strategies for effective use and implementation of quality indicators for medical professionals in the hospital.
- To adopt and/or develop strategies for the effective use of quality indicators by medical professionals in the hospital, applicable for Dutch hospitals, with special focus on information feedback and embedding of indicators in management systems.
- To develop methods (qualitative and quantitative) to measure quality improvement in clinical practise, in response to the use of quality indicators.
- To test the effectiveness of the developed strategies on the quality of care in selected areas in the hospital.

Strategic and innovative aspects
In the development of quality indicators for health care we can distinguish several phases. In the Netherlands we are at the stage in which indicators for health care have been developed, but not yet firmly implemented and tested on their effect. At this stage there is a great need to make effective use of quality indicators. RIVM can develop methods for optimal use of indicators which can also be adopted by other organisations in the implementation of quality improvement. The RIVM has been in a position in previous projects to develop indicators and in this project will make this next step towards its effective use. The RIVM is increasingly involved in projects on monitoring quality of care by using indicators. Also in the new exper-

3 The study will be carried out in close collaboration with Tilburg University (Tranzo). Tranzo is specialized in implementation/change strategies in care settings, with regards to infrastructure (e.g. cooperation with hospitals) and knowledge. This project relates to two other RIVM-research studies on performance measurement in health care. We will be in close collaboration with these projects.
tise centres at RIVM (e.g. CVB, Clb), indicators will be used for quality management. Therefore, it is important to increase knowledge on the optimal use of indicators at RIVM. This study will contribute to the development of this knowledge.

**Planned activities**

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

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

**Planned products**

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

**Foreseen follow-up**

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

Motivation

Over the last decade genomics, proteomics and metabolomics technologies have changed the field of toxicology enormously. Toxicogenomics is defined as the study of responses of the genome to hazardous substances, using 'omics' technologies such as genome-wide mRNA expressions (transcriptomics), cell and tissue-wide protein expressions (proteomics) and metabolite profiling (metabolomics), integrated with bioinformatics analysis tools and traditional toxicology. In various legal frameworks for (industrial) chemicals, but specifically in REACH, the use of toxicogenomics for risk assessment (RA) is anticipated. It is generally acknowledged that genomics data on their own are basically insufficient for risk assessment purposes, but genomics data can lead to the identification of the mode of action (MOA) and classification of chemicals. With toxicogenomics, a better understanding of mechanisms of toxicity can be achieved, and gene expression profiles can be identified that are representative of adverse outcomes prior to more time consuming and traditional measures. Furthermore, it is equally alleged that genomics information may well improve prioritization of risk of new chemicals based on expression profiles and biomarkers describing the potential toxicity of the chemical.

Aim of the project

The aim of this project will be to identify future opportunities and/or limitations of 'omics' technologies when applied to (improved) risk assessment strategies by:

- Inter-species extrapolations. We will perform exposure studies in rodent- and human cells and will use transcriptomics analyses to define and/or interpret differences and similarities in toxic pathways between the species.
- Comparison of toxicogenomics with other integrated test strategies. Within the compound category of phthalates we will substantiate or reject Q-SAR predicted potencies of the phthalate members using transcriptomics data.
- Dose-effect relationships of genotoxic versus non-genotoxic carcinogens. We will try to prove that thresholds of adverse effects of all chemicals exist, irrespective of their mode of action.

Strategic and innovative aspects

The role of genomic approaches in risk assessment today is negligible and research in this area is only in its infancy. The promising role of this technique for future implementation in and improvement of risk assessment warrants exploratory research by institutes with sufficient expertise in (toxico) genomics and risk assessment. The results of this project will give RIVM an excellent position to contribute to international activities already started by IPCS, OECD and US-EPA and several Toxicogenomics Centers (NCT, USA; NTC, NL). In Europe, the RIVM will be able to contribute to the development of integrated testing strategies needed in various regulatory frameworks such as REACH, the new European law for registration.

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4 This project is related to the projects: Genomics (SOR), CMR (VWS), "Development of high throughput toxicogenomics-based in vitro screens ..." (STW), "Mechanism based toxicogenomics ..." (STW) and project in FP6 and Nationaal regieorgaan genomics.
evaluation and authorization of chemicals, which will be implemented in 2009. This project will strengthen RIVM’s position in future expert advice to regulatory entities.

Planned activities

1. From literature and from public accessible databases, existing data for carcinogenesis and mutagenesis reference chemicals will be gathered. First we will focus on phthalates like di-(2-ethylhexyl)phthalate (DEHP) and others.

2. Interspecies- and in vitro similarities and differences of toxicogenomic datasets will be evaluated. Data that are not available will be obtained from the following experimental objectives:
   - Inter-species extrapolation.
   - Comparison of toxicogenomics with other integrated test strategies.
   - Dose-effect relationships of genotoxic versus non-genotoxic carcinogens

Planned products

- Improved risk analysis protocols for toxic compounds (of all CMRI categories), as well as for drugs.
- Improved expert advice to regulatory entities.
- Contribution to the development of guidelines by international organizations (EU, OECD, EPA, ICH).
- Strong position of RIVM in the EC and other international frameworks.
- An international workshop focussed on the use of “omics” technologies in risk assessment will be organized during course the project period.
- Scientific papers in peer-reviewed journals. Improved opportunities to secure externally-supported projects.

Foreseen follow-up

The laboratories of RIVM/SIR and RIVM/SEC will be able to perform an improved, more mechanism-based risk analysis of chemicals. But also for the risk assessment of drugs, the information gathered in this project will be very valuable (for RIVM/BMT). The knowledge obtained in this project will lead to the development of a workgroup/forum on toxicogenomic answers for future risk assessment problems and gives RIVM an excellent position to contribute to international activities such as already initiated by IPCS, OECD and US-EPA, National Centre of Toxicogenomics of NIEHS (NCT), 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.
**Motivation**

Only a small number of Dutch citizens meet the dietary recommendations such as the guideline to consume less than 10% of saturated fat and the guideline to consume more than 200 grams of vegetables daily. As a result, the overall health loss caused by the discrepancy between the current and the desired diet for the Dutch population is comparable to that caused by smoking: i.e. an annual loss of 300,000-400,000 DALYs (disability adjusted life years). Experts predict that trends in eating habits and in the types of food available on the market during the coming 15 years will result in an even greater health loss. Good methodologies for dietary risk assessment are thus essential for an adequate policy aimed at a healthy nutrition and safe foods, and consequently, important for public health.

**Aim of the project**

The project aims to develop statistical methodologies for improved dietary risk assessment. The specific objectives are:

- Further development of statistical methods to transform data from dietary monitoring (on actual intake over a short period) to biologically relevant data on habitual intake;
- Further development of probabilistic methods for the combination of consumption (and composition) data from various sources. (e.g. consumption or purchase data on specific foods with data on overall diet). These methods give insight in uncertainties and allow more optimal use of the various data at hand;
- Development of guidelines for exploring dietary data before analyses: how to deal with sample bias, extreme values, distributions that cannot be transformed to normal.

**Strategic and innovative aspects**

The project proposes an innovative approach to improve existing statistical methodologies for dietary exposure assessment. This will enable RIVM to extend its role as a key player in the development of methodologies for analyzing food consumption data. This knowledge will strengthen RIVM's national and international position in this field. Nationally, intensive cooperation is planned with Wageningen University, TNO Quality of Life, RIKILT, and IRAS. One of the goals of the national cooperation is to enhance the international position regarding exposure modelling in relation to healthy nutrition and food safety issues. The project will provide the tools to elucidate certain questions of policy makers that can not be answered at this moment and will thus enable acquisition of new assignments.

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5 The project is related to the 'National food consumption surveys' and will develop further on methodological problems encountered in the project 'Evaluation of micronutrient intake'. International collaboration will be undertaken in the EFCOVAL-project (European Food Consumption Validation).
Planned activities

It has been recognized that there are major differences in dietary modelling with respect to nutrients and food chemicals, but that in the future modelling principles can be harmonized. The methods that will be developed will therefore be applied to examples in the fields of nutrients as well as food chemicals.

The project concerns activities in three subtopics:

1. Transformation of collected data on actual intake over a short period of time to distributions of habitual intake.
2. Probabilistic methods for the combination of consumption (and composition) data from various sources.
3. Guidelines for exploring dietary data before analyses: how to deal with sample bias, extreme values, distributions that cannot be transformed to normal.

National as well as international collaboration on this topic will be intensified.

Planned products

The following products will be produced:

- A report on ‘Inventory of needed improvements and extensions to methods to transform actual intake into habitual intake, and probability approaches’
- Extensions to software for transformations to habitual intake (if needed)
- PhD-Thesis on ‘statistical methods for use on dietary monitoring data’
- A number of publications in peer reviewed journals
- Guidelines for exploring dietary data before analyses (publication for journal or on the internet)

Foreseen follow-up

The statistical methodologies developed can be applied in future assignments by the Ministry of Health, Sports and Welfare, the Food and Consumer Product Safety Authority of the Netherlands, the European Food Safety authority or similar organisations from abroad.
Motivation

Nanotechnology (NT) is the design, characterization, production and application of structures, devices and systems by controlling the shape and size at the nanometer scale. New nano-sized materials may be used in cosmetics, pharmaceuticals, medical technology products, household products like paint and food technology. The small size is accompanied by special characteristics such as increased chemical and physical (re)activity. This main specific characteristic also allows the potential interaction of nanoparticles (NP) at subcellular level. Recently there has been an increase in the awareness that the production and use of NT products may be accompanied by both environmental and health risks. Although current methodologies are useful for evaluating certain risks of NT products, it is expected that not all potential risks of NT will be covered. So, new methods need to be developed. An integrated approach is needed for hazard identification and risk evaluation for man and environment, including chemistry, cell biology, (eco)toxicology, pathology, (toxico)kinetics, and modelling.

Aim of the project

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

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

Strategic and innovative aspects

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

In view of the growing development and application of man-made engineered NPs, in the next decades many questions about the hazards and risks of NPs need to be answered. RIVM

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6 External partners are the University College Dublin, Dublin, Ireland; Ghent University, Belgium; Radboud University, Nijmegen, Maastricht University, Maastricht. Several RIVM-projects on risks of nanotechnology are related to this project.
wants to be one of the Institutes providing answers to both policy makers and the public on safe use of Nanotechnology.

**Planned activities**

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

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

**Planned products**

- Peer reviewed publications
- 2 PhD theses

**Foreseen follow-up**

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

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

The whole of the EU will benefit as adjusted risk assessment methodologies are urgently needed to allow for a proper risk assessment. It has even been suggested to use the precautionary principle and ban all applications of nanoparticles until all is known on risks of engineered NP and sound safety evaluations have been made available.
Title: Alternatives for Animal Testing

Project number: S/340050 (VGC.27)

Project leader: Dr. A. Opperhuizen (TOX)

Start: 01-01-2007

End: 31-12-2010

Total costs: € 804,000

Motivation

Over the last decades animal testing has played a crucial role in hazard identification and risk assessment of chemicals and drugs. As such animal testing contributed significantly to the prevention of adverse health effects to humans. However, public opinion and the political arena have put pressure to reduce the use of animals for toxicity testing. Considerable effort has been undertaken to develop and to implement alternatives for animal testing. Reduction, refinement and replacement, the so-called 3 R’s concept, is the key element of this political and scientific effort. As a result, many useful adjuncts to toxicological tests have been developed, and in some cases validated and finally implemented. However, in many other cases validating research is still ongoing. With the adoption of the REACH program in the EU in which many thousands of chemicals need to be evaluated; even more pressure on the implementation of alternative tests has arisen. There is pressure to fully replace animal testing, as already has been decided in the field of testing cosmetics products. This RIVM project not only intends to contribute to the further implementation of the 3 R-approach in hazard and risk assessment, but also contributes to improve the quality of these assessments.

Aim of the project

The aim of the current project is to identify possibilities but also fundamental limitations for the replacement of in vivo animal tests for detecting carcinogenic, mutagenic, reproduction- or immune toxic (CMRI) hazards. Specific attention will be given to adapt (mimic) pathophysiological pathways within the alternative methods. Specific objectives:

- To identify general pathways of CMRI toxicity irrespective of modes of action of specific chemicals.
- To find cellular responses for specific modes of actions, and accompanying (gene) markers, which indicate where toxic effects become irreversible and adverse effects become inevitable.
- To evaluate, where replacement with in vitro alternatives are impossible, the possibilities of using above mentioned early (toxicogenomic) markers to at least reduce the duration of in vivo experiments (refinement), or to limit the numbers of animals needed.
- To combine QSARs and PBPK modelling with early marker data for hazard identification and risk assessment.

Strategic and innovative aspects

This projects aims to combine state of the art techniques, like rodent genetics, genomics, bioinformatics, in vitro cell technologies, in new generation toxicology risk assessment. The ambition of the project is the development of future alternative test methods to improve risk assessment using less, or no laboratory animals at all.

7 Collaborating partners in the project are WUR, (Wageningen), Leiden University Medical Center, Utrecht University, TNO, Zeist. Several RIVM-projects on toxicogenomics are related. The outcome of this project will be linked with two other SOR projects (Toxicogenomics in Risk Assessment and Integrated Testing Strategies for Risk Assessment of Chemicals - ITS)
Planned activities

1. From ongoing (externally funded) studies we will collect many genomic data on CMRI-related toxicological effects. These data will be used, within this current project, to identify, using toxicogenomics and bio-informatics technologies, common pathways of toxicity induced by CMRI compounds. Critical (bio)markers or even whole biochemical pathways will be identified to be used as early qualifiers of adverse effects.

2. For a few new reference chemicals, representing all CMRI-classes, such early markers (qualifiers) will be further evaluated making use of toxicogenomics in experimental animal studies.

3. Information of toxicogenomic/bio-informatics data and that of other early markers will be used to evaluate data obtained from in vitro experiments that have already been used as surrogates of the in vivo studies.

4. If the fundamental limitations of in vitro assays will be illustrated, because critical phases of the pathophysiology may not be mimicked in vitro or by modelling, we will put effort in developing new in vivo tests systems, like the sensitized mouse models with the aim to reduce animal use and to refine current tests.

Planned products

- Test protocols will be proposed which represent the state of the art of hazard testing of compounds.
- At least 8 peer reviewed papers are expected as a direct result of this project
- An international workshop or symposium
- In conjunction with the Netherlands Toxicogenomics Center (NTC) at least 4 PhD theses will be delivered in this field (cofinanced by STW, ZONmw and NTC).

Foreseen follow-up

Reduction of animal testing is one of the important political issues in the field of risk assessment of chemicals and agents. Despite the pressure this generates on the scientific community, a large variety of alternative methods will come available in the upcoming years. However, it is clear that in the next few years much funding is required to develop and validate adequate methods. As budgets are always limited, there is a serious risk that alternatives are introduced and implemented or required by law, which insufficiently identify the potential hazard for man and environment. Therefore the Dutch as well as international government favour most from this project. The project will provide an excellent basis for future activities in the field of risk assessment (using alternative methods), and in selecting new alternative methods. Furthermore it will provide a good basis for acquisition of funded validation testing. The international status of RIVM in the field of alternatives for animal testing of hazardous agents will be further improved.
2 Emergency Response Functions and Safety (ERF)

The theme of Safety has rapidly gained (inter)national attention and RIVM has to develop new expertise in this field. Emergency Response Functions and Safety are important subjects within two RIVM research sectors. Several threats (chemical, biological and radiation) and accidents require a sensible preparedness and adequate response. From a biological point of view biological safety and outbreak management demand attention. From an environmental view, modelling of environmental quality (chemicals, radiation, and terrorism) and toxicological effects in humans are topics of particular interest.

<table>
<thead>
<tr>
<th>Project number</th>
<th>Title</th>
<th>Author</th>
<th>Costs (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S/330006</td>
<td>Biothreat DNA Micro-arrays</td>
<td>Van Rotterdam</td>
<td>1,365,640</td>
</tr>
<tr>
<td>S/620001</td>
<td>QRA: Instrument for Safety Policy</td>
<td>Uijt de Haag</td>
<td>1,084,380</td>
</tr>
<tr>
<td>S/610003</td>
<td>ERFRAD: Emergency Response Function for Radiation</td>
<td>Twenhöfel</td>
<td>640,000</td>
</tr>
<tr>
<td>S/630007</td>
<td>Rapid Assessments after Disasters</td>
<td>Grievink</td>
<td>768,000</td>
</tr>
<tr>
<td>S/660001</td>
<td>Research Cooperation in Human Toxicology</td>
<td>Meulenbelt</td>
<td>1,001,200</td>
</tr>
<tr>
<td>S/609001</td>
<td>Exposure Testing after Terrorist Attacks</td>
<td>Hoffer</td>
<td>250,000</td>
</tr>
<tr>
<td>S/609002</td>
<td>From Sub-acute to Acute Response</td>
<td>Van Belle</td>
<td>600,000</td>
</tr>
</tbody>
</table>
Biothreat DNA Micro-arrays

Project number: S/330006 (Cib.05)
Project leader: Dr. B.J. van Rotterdam (MGB)
Start: 01-01-2007
End: 31-12-2010
Total costs: € 1,365,640

Motivation
Accurate, simultaneous detection of a wide range of pathogens is highly desirable for clinical diagnostics, but also for a rapid response to the threat of bioterrorism. Pathogen identification based on nucleic acid amplification strategies avoids the requirement for culturing the organism (which is laborious, time-consuming, and expensive). Moreover, such molecular assays can directly characterize virulence factors and are exquisitely sensitive, accurate, and rapid. However, as successful identification depends almost entirely on appropriately chosen primer sets, all PCR based testing requires a priori knowledge of the identity of the contaminating organism(s). Consequently, there is a critical need for a diagnostics system able to detect both known and unanticipated pathogens. DNA microarrays, which enable the simultaneous interrogation of thousands of genetic elements, offer these parallel and high-throughput screening capabilities. While microarrays may offer broad screening, selectivity and speed, important challenges remain in obtaining the desired sensitivity that is required for pathogen detection in complex samples. This results from the low quantity of pathogen DNA and the inhibitory effects of complex environmental matrices on enzymatic activity and fluorescent reporters. For most sample types, some sort of amplification will be required to dilute inhibitory compounds and/or to provide sufficient copies of pathogen gene markers for detection by microarray hybridization.

Aim of the project
We aim to significantly enhance the ability to detect multiple (pathogenic) micro-organisms in complex samples by applying DNA microarray technology for diagnostic purposes. This will greatly increase the range of organisms and virulence factors that can be screened for simultaneously, thereby increasing the detection confidence and allowing the detection of unanticipated pathogens. Two microarray formats will be developed and evaluated for the detection of a number of selected bioterrorism agents. The detection will be challenged by low DNA concentrations and inhibitory effects of complex environmental matrices. Therefore, we will develop methods for amplifying target DNA which will increase sensitivity and minimize the effect of inhibitors. In addition, different labelling protocols will be compared to maximize detection.

Strategic and innovative aspects
The project will follow up on the well documented international trend to use micro-array technology for detection and typing of micro-organisms. The anticipated impact will be a broader and more confident screening for bioterroristic agents, which could even turn out to become quicker and cheaper compared to current methodology. The proposed research will incorporate various developments in the exciting and rapidly evolving field of microarray technology. By combining this technology with unbiased DNA amplification (Whole Genome Amplification, on-chip DNA amplification) and novel labelling methods, new applications for

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8 On the European level collaboration on this topic is already in place within the EU COST action "Array technologies for BSL-3 and BSL-4 pathogens". Further experimental collaborations will be setup with Novel and Dangerous Pathogens Dept, Health Protection Agency, Porton Down, UK. Collaboration on array technology within the Netherlands has been initiated with the Microarray Department, Univ. of Amsterdam. New collaborations will be set up.
pathogen detection technology will be explored. In addition, the development of a platform for simultaneous detection of multiple biothreat organisms will greatly enhance the capabilities for accurate detection of such organisms within the national response organization and can easily be adapted for other applications such as detection of Genetically Modified Organisms (GMOs) in food and feed and screening of clinical samples.

Planned activities

1. Potential gene targets for detection of Biothreat pathogens will be selected from literature and public databases. The targets will be evaluated for their selectivity and suitable control sequences will be identified as well. Suitable target sequences will be cloned and used for optimization and control purposes. Because micro arrays require DNA of high quality, methods for checking DNA quality will be tested.

2. For both microarray formats, an array will be designed for the detection of the selected targets. For the spotted microarrays this will entail the design of oligonucleotides of appropriate length, with similar optimal melting temperatures and without significant secondary structure. Hybridization conditions need to be optimized. The probes (‘common’ and ‘discriminating’ probes) used in the ligase detection assay need to be designed such that they selectively hybridize to the desired target sequences. The selectivity and potential sensitivity of the developed arrays will be evaluated by using cloned target genes and DNA extracted from the selected organisms and from related control organisms.

3. Methods will be investigated for increasing the sensitivity of assays. In order to increase the amount of target DNA and minimizing the effect of inhibitors, we will use a non-biased amplification of DNA by using whole genome amplification (WGA), followed by DNA fragmentation, labelling and hybridization to microarrays. For increasing the sensitivity of the oligonucleotide arrays, we will investigate the possibility of on-chip DNA amplification (i.e. amplification after hybridization), e.g. by rolling circle amplification.

4. Finally, different labelling protocols will be compared. Of particular interest will be the development of direct labelling of DNA resulting from WGA [e.g. by using Kreatech technology]. Throughout the development of the arrays, bioinformatics tools will be tuned for reliable processing of and easy access to the generated data.

Planned products

- Two microarray platforms for the detection and typing of selected biothreat agents.
- Protocols for sample pre-treatment, signal amplification and labelling strategies to allow for sensitive detection of BT agents from diverse environmental matrices.
- A framework of experience, protocols and tools necessary for further developing and updating of these platforms and methods.
- Publications in peer reviewed international scientific journals.
- Presentations on international meetings and symposia.

Foreseen follow-up

The technique will be implemented in the screening of suspect objects and soil/water/surface samples on the presence of bioterroristic agents within the National Laboratory Response Network and the Environmental Incident Service. The methods will be developed for detection of biothreat agents, but could be adapted for detection of pathogens of clinical or food-safety relevance.
Title: QRA Instrument for Safety Policy

Project number: S/620001 (MEV.29)
Project leader: Dr. P.A.M. Uijt de Haag (CEV)
Start: 01-01-2007
End: 31-12-2010
Total costs: € 1,084,000

Motivation

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

Aim of the project

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

Strategic and innovative aspects

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

Planned activities

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

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9 The project is linked to a number of other projects, like projects of Dutch and EU working groups and other SOR-projects (CFD modeling of the environment and Evaluation of safety measures, both 2005-2006).
An overview will be made of existing methods to quantify the important aspects of the Safety Management System and the effect of preventive risk reducing measures, including methods like Safety Integrity Level classification and Layer Of Protection Analysis. Also the application of fault tree and event tree modelling will be evaluated.

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

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

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

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

9. Development of a method to incorporate location-specific characteristics in the valuation of mitigating measures
Based on the CFD results, guidelines are drafted to describe the influence of location-specific characteristics on the hazard zones and their impact on mitigating measures.

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

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

Planned products

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

Foreseen follow-up
The results of the project will be valuable to the Dutch government and, of course, to the society, since it will aid in implementing cost-effective measures.
The demonstration of the principles of this improved QRA method will follow-up in the elaboration into a complete QRA method that is accepted for spatial planning in the Netherlands.
Motivation
During large scale nuclear and radiological emergencies quantitative risk estimates are a decisive factor in the determination of an effective countermeasure strategy. In view of the large social and economical impact of countermeasures, reliability and a timely availability of the underlying risk estimates are important attributes. Risk estimates, based on model calculations have been developed for many years and have found there way into the operational emergency management centres. However the model calculations lack sufficient accuracy of prognosticated doses when based only on estimated guesses of model input parameters. Methods that exploit the advantages from modelling approaches and the results from radiological measuring networks and environmental surveillance programs provide for a more promising estimator for projected doses and definition of intervention areas. The resulting quantitative risk estimates in nuclear and radiological emergency management have become a highly collaborative product of multi-disciplinary assessment teams. In order to reach coherence in the approach and response from the different expert groups it has become clear that, the integration of domain specific information and harmonisation of modelling approaches are important and non-trivial requirements for an integrated advice. Considering the wide spread dispersion of radioactive material over many nations after a nuclear accident it is further evident that coherence in emergency management response is not only required nationally but also on the European level.

Aim of the project
The overall aim of the ERFRAD project is to enhance coherence in the response and methods of off-site nuclear emergency management and extend technical capabilities in radiological assessments of the Back Office Radiological Information (BORI) by the development of fast and reliable methods supporting integrated quantitative risk estimates based on optimised analyses of model approaches and radiological measurements. Specific objectives are nationally and internationally targeted:

National:
• Improve the prognostic quality and enhance integration of radiological assessments from expert groups on meteorology, radiological measurements, urban and agricultural environments and food production systems.
• Optimization, integration and extension of models allowing timely and reliable risk assessments with quantifiable uncertainty estimates.
• Extension of modelling approaches from strictly environmental evaluations to decision supporting assessments aimed at optimising countermeasure strategies.

International:
• Contribute to a coherent and harmonised response to nuclear emergency management in Europe by collaboration with the European expert groups in peer reviewed scientific programs.
• Strengthening the international operational decision support network by joining forces with existing R&D and user groups in Europe and implement successful modelling and analyses approaches.
Strategic and innovative aspects

Nuclear accidents with considerable releases to the environment (e.g. reactor accidents) are known to give rise to transboundary issues between states. Off-site nuclear emergency management therefore requires an international approach. Harmonisation, communication and a coherent response to nuclear emergency management are already important research topics in the European Union. This research is currently concentrated in the EURANOS European R&D project on nuclear emergency management. Requirements for decision support at RIVM seem to be in line with the demands of the operational emergency management groups participating in the EURANOS program. A European collaboration and evaluation of European decision supporting systems may therefore have a significant spin-off on the development of RIVM's emergency response function (ERF) on radiation. Furthermore the international decision support user groups are shifting interest to the chemical and biological domains. In particular this can have considerable spin-off for the chemical and biological ERF's at RIVM.

Modelling approaches are not new by themselves but the integration and applicability within the national and international (European) context in the nuclear emergency management domain are of innovative nature. The applicability of uncertainty analyses in numerical weather prediction ensembles as a means to assess uncertainty in geo-referenced radiological risk estimates is unprecedented in Europe. Here RIVM in close collaboration with KNMI may obtain a leading position in the field.

Planned activities

1. Establishing working groups with national and international partners, specifying objectives and working packages on quantitative risk estimates. Evaluate existing model approaches and decision support system functions.
2. Evaluate models and decision support functions supporting coherent multi-disciplinary radiological assessments, define conditions for use, adapt existing models for use at RIVM.
3. Evaluate and develop methods for integrated analysis using advanced data assimilation and geo-statistical interpolation techniques.
4. Evaluate uncertainty in risk estimates and its communication.

Planned products

- Evaluation of existing modelling approaches
- Feasibility studies
- Validation of data assimilation approaches
- Mapping techniques for contaminated urban and rural environments.
- Quantification and visualisation of uncertainty in radiological risk assessments
- Several publications

Foreseen follow-up

Scientific result of this project is directed towards enhanced capabilities of technical evaluation and assessment of nuclear and radiological emergencies in the Netherlands and Europe. This project will strengthen the strategic position of the Back Office Radiological Information and therefore the ERF on radiation of RIVM as an expert institute in (technical) off-site nuclear emergency management. Part of scientific program of this project may have considerable spin-off to the chemical and biological emergency management domains.

\[\text{The project has a close relation to international projects, like the EURANOS, and to other national and international research programs on air dispersion, data assimilation and uncertainty in weather prediction models.}\]
Title: Rapid Assessments after Disasters

Project number: S/630007 (MEV.35)

Project leader: Dr. Ir. L. Grievink (MGO)

Start: 01-01-2007

End: 31-12-2010

Total costs: € 768,000

Motivation

The role of the government after disasters is to protect and restore public health. Following a disaster, health care workers and decision makers need adequate information on possible (negative) health effects due to exposure or other disaster related events. In addition, the stakeholders request rapid insight into health status and health care needs. In the decision making process, rapid assessment methods are needed to collect information that is immediately required for decision making. Furthermore, information that is not collected soon after a disaster might be irretrievable, or biased when collected later. The possibilities of a long-term health impact assessment have to be considered already in the acute response phase, and information on exposure needs to be collected accordingly. There is a need for a coherent package of rapid assessment methods for application in technological and natural disasters in the Netherlands.

Aim of the project

The overall objective is to improve public health decision making immediately after disasters. This project provides an essential tool to contribute to public, environmental and occupational health decision making. Specifically, we will develop a coherent set of rapid assessment tools after disasters, consisting of:

- An exposure assessment tool for radiation, nuclear and chemical agents
- An exposure assessment tool for experiencing shocking events
- Health status and needs tool.

Strategic and innovative aspects

The study is an in depth elaboration of the usual work package of CGOR. It will strengthen the future role and position of CGOR and the Centre for Health, Environment and Safety (cGMV) in (inter)national perspective. Innovative is the development of methodology to assess 'exposure' to shocking events. Coherent package in which both physical and psychosocial aspects of exposure are incorporated in the tools; currently available rapid assessment tools cover only part of the information need. New methods for the disaster emergency response in Netherlands with which information can be collected rapidly.

Planned activities

1. Rapid exposure assessment to chemical agents or radiation
   Review of the literature, develop criteria for methods and liaise with CIb for biologic agents.
2. Rapid exposure shocking events
   Data analyses plan, data analyses, development questionnaire, test & validate method.
3. Rapid health assessment, a quick win
   Translate and adjust existing method/ checklist of WHO to the Dutch situation,

Related projects are Exposure testing during terrorist attack (SOR project MEV-38), Flash Environmental Assessment Tool (IMD; project number E/609000/01). Small Area Health Analyses: A Geographic Toolkit (SMARHAGT, SOR project MEV-20).
4. Rapid health status & needs assessment
   Interviews with stakeholders, literature review of existing methods, development of method.

Planned products

- Criteria for methods of exposure assessment
- Questionnaire for determining shocking events
- Overview of methods for health needs and status
- Method(s) for health needs and health status assessment
- A checklist for public environmental health professionals
- Several scientific papers and literature reviews

Foreseen follow-up

Based on the current national and international knowledge and experience, this project will develop a coherent package of rapid assessment methods for public environmental health professionals (GHOR) at the level of municipal health departments. After training of the GHOR, the information of the developed package of methods or parts of it can help to make immediate decisions during the response and aftercare phase after a disaster. The application potential of the developed methodology clearly extends beyond the Dutch setting, at least to other European countries.
Motivation

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

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

Aim of the project

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

Strategic and innovative aspects

In contrast to pharmaceuticals knowledge on human toxicological issues (with focus on inter-individual effect variability based on polymorphism in metabolism and individual target organ susceptibility for xenobiotics) is limited for chemicals. With this knowledge a more accurate acute human effect assessment after exposure to chemical substances is possible and better advice about poisonings can be provided. This knowledge will clearly improve the poisons response function. The achieved knowledge also enables the development of more precise effect assessments for exposure intervention guideline levels.

Collaboration in research with the NFI will increase the possibilities to exchange knowledge on clinical en forensic toxicological issues between the institutes. A more formalised research cooperation with IRAS of the University Utrecht increases the possibility to spend research budget more accurately.

Planned activities

1. PhD 1: Study on human variability in biotransformation with focus on enzymes involved in the metabolism of THC (and other cannabinoids) and some designer drugs.

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12 The project is related to SOR-project “Exposure testing after terrorist attacks”
Performing primarily *in vitro* or if necessary *in vivo* animal or human studies on different enzymes related to the metabolism of cannabis and some designer drugs.

2. PhD 2: Study on human variability in target organ susceptibility (e.g. expression, function and regulation of receptors and receptor drug interaction) of cannabinoids and some designer drugs.

Performing *in vitro* or if necessary *in vivo* animal studies on cannabis receptors to investigate differences in responsiveness because of polymorphism of cannabis receptors and some designer drugs.

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

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

**Foreseen follow-up**
This research will strengthen the position of the poisoning response function and consequently the emergency response function. Furthermore, the research network between RIVM, IRAS and NFI in the field of clinical and forensic toxicology, will strengthen other RIVM research programs such as on medicines and functional foods, and environmental quality and public health.

It is anticipated that with the achieved knowledge the funding for new projects can be obtained.
Title: Exposure Testing after Terrorist Attacks

Project number: S/609001 (MEV.38)

Project leader: Dr. S. Hoffer (IMD)

Start: 01-01-2007

End: 31-12-2008

Total costs: € 250,000

Motivation

In case of a terrorist attack with chemical agents two specific situations may arise in which human sampling can provide vital information to the health professionals. The first situation includes symptoms without a known cause. One or more subjects may develop symptoms while it is unclear if, and if so, which chemical agents are responsible. The second situation comprises subjects that may have been exposed to a known toxic compound, but data with regard to the extent of the exposure is lacking. In addition to clinical information like symptoms, data of human specimens may then be very helpful in estimating the level of exposure. This requires accurate, quick, and reliable analysis techniques. Techniques to rapidly screen and analyse human specimens on a broad range of toxic xenobiotics, are however poorly integrated. Even within the Dutch National Laboratory Network (acronym LLN-TA) which ensures an effective laboratory response to CBRN terrorist attacks and has the analytical capacity to deal with issues concerning suspect objects of (allegedly) chemical and biological nature, this expertise is lacking.

Aim of the project

Aim of the project is to develop a rapid toxic screen that can be applied after a terrorist strike with chemical agents. The ultimate goal of this research project is to rapidly and accurately detect and identify toxic substances used in a terrorist attack by doing analyses of samples of human materials. The overall purpose is to provide exposure information to health officials and physicians to help prevent diseases that results from exposure to chemicals. This will be achieved by analysing clinical samples to identify or verify the chemical agent(s) released and semi-quantify the levels of exposure for an individual, in order to determine the prevalence of people with levels above toxicity levels, but also to identify cases of non-exposure. For this, broad-spectrum screening methods for human specimen, as well as a strategy will be developed.

Strategic and innovative aspects

There is a lack of a broad-scale screening strategy and analysis methods for human specimens like blood, urine and nose wipes that can be called upon whenever a chemical terrorist act occurs in the Netherlands. Only recently, the CDC in the United States also started the development of a rapid toxic screen that addresses the issues of chemical exposure testing after terrorist attacks. This proposal combines the best of knowledge with respect to risks for intoxication and multi-analyse chemistry within the RIVM and the Netherlands. Furthermore, this project will strengthen the position of the RIVM and the Netherlands; within the structures responsible for preparedness and response in case of a terrorist attack in the Netherlands.

13 RIVM is partner in the Dutch National Laboratory Network (LLN-TA) as are TNO D&V, NFI, Rikilt, Douanelaboratorium, Kiwa Water Research, CIDC Lelystad and VWA,

14 The project is related to two other SOR-projects (Research Cooperation in Human Toxicology; Rapid assessments after disasters).
Planned activities

1. Assessment that deals with the inventory of priority chemical agents, their metabolites in human specimens, and the toxicologically relevant concentrations. Considered in the selection: i) agent threat lists both national and international, ii) matrix properties, iii) agent characteristics and iv) symptoms.

2. A performance assessment of the available RIVM equipment that is able to detect the selected threat agents and the evaluation of expertise in the Dutch National Laboratory Network and some relevant hospitals. This will result in an overview of the strengths and weaknesses in analytical expertise when responding to a chemical terrorist attack.

3. Development of analytical screening strategies to the specifications using the results from the assessments from phase one. Effective methods that are already available will be integrated. Halfway the project a pilot experiment will be performed using human specimens spiked with either chemicals or metabolites. Discussions with the CDC.

4. Integration of the strategy and writing of an outline for a decision support tool. Submission of report which addresses the results obtained so far and when applicable the future challenges.

Planned products

- A select list with priority chemical agents and their metabolites in human specimens.
- An inventory of analytical toxicological methods already present within the Netherlands, involving their applicability, sensitivity, specificity, and speed in case of a terrorist attack. In addition, a comparison with international analysis methods.
- An overview of gaps in expertise and the set up of performance specifications of the screening assay based on available equipment to address these gaps.
- The design and validation of a screening strategy in which methods will determine intoxication levels of the selected chemical agents in human specimens.
- An outline of a decision support tool for the national laboratory response capability for applying state-of-the-art technologies to verify human exposure to hazardous chemicals.
- Publications in at least two peer-reviewed publications and presented at symposia and conferences.
- A report that will include all the results from this project and if necessary future research needs will be defined.

Foreseen follow-up

The development of the screening method for the analysis of human specimens will also take into account the option of a field analysis. This means that during the development of the screening strategy, specifications for applying this screening in a mobile laboratory will be considered.

Since this project will only cover a small portion of the toxicological analysis, future research is required to cover the entire field. In addition, the results from this project will also be beneficiary to the analysis of clinical samples from accidents in which civilians, first responders or military personnel in missions have been exposed to unintentionally released chemicals. This outcome may lead to new assignments or further funding by for instance the Ministry of VWS or the Ministry of Defence.
Motivation
The main goal of the Environmental Incident Service (MOD) of the RIVM is exposure assessment during incidents as large spills and fires. With this, the service can provide a realistic risk assessment for the local authorities in an early stage. However, a substantial time gap exists between the beginning of the incident and the start of the measurements, mostly between three and six hours. Because of this, the exposure assessment during the starting period of the incident is always a problem. It is expected that the concentration of air pollutants in the first phase of the incident near a fire could be high enough to affect the health of exposed citizens. This cannot actually be proved because measurements of the acute phase are always lacking.
To obtain measurement results from the beginning of an incident measurement tasks could be carried over to the local authorities. When new and better sampling and measurement strategies and methods are made available to them the quality of the exposure assessment made by the RIVM can improve dramatically. To achieve good results, a lot of effort has to be put in the formulation of rugged and easy to operate methods.

Aim of the project
The primary aim of the project is improving the human and environmental exposure assessment to Hazardous Airborn Pollutants (HAP) during incidents. This will be done by reducing the lag time between the start of the incident and the beginning of the extended measurements. This new approach means that high quality measurements in the environment will be performed over a longer period during the incident. This will give the MOD the opportunity to make a better risk assessment and it will improve the quality of the advises that the MOD delivers to the government and the local authorities. To achieve this, we will do research on rugged and easy to use sampling and analysis techniques and strategies. The main objective of this is incorporating the techniques within the first response organisations in combination with the MOD. To check the effectiveness of the techniques, we will work in a pilot with some fire brigades to test the methods in the field.

Strategic and innovative aspects
Collecting high quality samples and performing high quality environmental measurements of exotic and complicated compounds during the first phase of an incident is rather new. Until now, the used methods and strategies are of limited use for performing exposure assessment. By carrying out this project, the RIVM will end up with a strong position in this field. This will not only be the case within the Netherlands but also in the international context.

Planned activities
1. Analysis and definition of the expected features of the measurement strategies and equipment and subsequent selection of the best strategies and equipment
2. Working visit to other country emergency services (Germany, USA)
3. Field testing of materials and methods
4. In-field operational pilot study of materials and methods

The project is related to the SOR-project Rapid assessment after disasters (DISASTERS)
5. Delivery of a complete method for integral exposure assessment

**Planned products**

- A complete set of environmental measurement strategies and methods.
- Three RIVM-reports
- Presumably three scientific publications.

**Foreseen follow-up**

After a successful pilot period the aim is that the strategies and methods are adopted by the emergency response in the Netherlands.
3   Infectious Diseases (INF)

The theme Infectious Diseases potentially covers all research questions, ranging from source of infection to effective intervention. Although most of the potential work will fit best in the sector of CIb (Centre for Infectious Disease Control), also food safety issues are relevant, especially on the level of sources of contamination. Immunology, vaccination and genetics are specific areas that need to be strengthened within RIVM. Besides this, effect studies and modelling issues are important.

<table>
<thead>
<tr>
<th>Project number</th>
<th>Title</th>
<th>Author</th>
<th>Costs (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S/230136</td>
<td>Whole Genome Analysis of M.tuberculosis</td>
<td>Van Soolingen</td>
<td>562,700</td>
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<tr>
<td>S/230146</td>
<td>Immunomodulation by Helminth Molecules</td>
<td>Pinelli</td>
<td>463,500</td>
</tr>
<tr>
<td>S/230406</td>
<td>Host-response to RSV (Respiratory Syncytial Virus)</td>
<td>Janssen</td>
<td>1,199,400</td>
</tr>
<tr>
<td>S/230416</td>
<td>Immune Pathways in Vaccination</td>
<td>Van Binnendijk</td>
<td>1,102,940</td>
</tr>
<tr>
<td>S/230426</td>
<td>Memory Immunity</td>
<td>Buisman</td>
<td>1,525,200</td>
</tr>
<tr>
<td>S/230436</td>
<td>Microarrays to Map Pertussis Adaptation</td>
<td>King</td>
<td>1,125,840</td>
</tr>
<tr>
<td>S/230446</td>
<td>B.pertussis Adaptation to Vaccination</td>
<td>Mooi</td>
<td>459,944</td>
</tr>
<tr>
<td>S/210026</td>
<td>Modelling the Future of MRSA in NL</td>
<td>Grundmann</td>
<td>342,750</td>
</tr>
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<td>S/210036</td>
<td>Tracking Emerging Epidemics</td>
<td>Wallinga</td>
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<tr>
<td>S/210046</td>
<td>Epidemic Modelling of Molecular Data</td>
<td>Wallinga</td>
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Motivation
In the last decade several DNA fingerprinting methods have been used to study transmission of tuberculosis (TB), as well as the phylogeny of the causative agent; Mycobacterium tuberculosis. One of the apparently most clonal groupings of M. tuberculosis is the Beijing genotype family. Recently, a worldwide survey revealed that Beijing strains are emerging often associated with drug resistance, more virulent in animal models and associated with relapse of tuberculosis. Currently, the most important question is how recently the Beijing genotype strains started spreading and how clonal strains of this genotype family are. Furthermore, the differences between the emerging modern Beijing lineage and the ancestral Beijing lineage need to be investigated. To answer these questions, Beijing genotype strains of the ancestral and the modern lineage should be compared by whole-genome sequencing.

Aim of the project
There are two specific aims related to this project:

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

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

If the findings in this project are in agreement with the expectations, whole genome sequencing will increasingly be explored in the research and diagnosis of infectious diseases the future.

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

Planned products
1. Revelation of the entire genome sequences of 15 *M. tuberculosis* isolates of various lineages. This will add significantly to the scientific community, where currently only two *M. tuberculosis* genomes are available.
2. Insight into the evolutionary development of the genome of *M. tuberculosis* under the pressure of human-to-human passage in a 15-year period.
3. The possibility to use genetic changes anywhere in the genome of *M. tuberculosis* to trace exact transmission routes of (genetically slowly changing) *M. tuberculosis* strains in the community. Ideally, the primary-, secondary-, and tertiary- sources of infection in TB epidemics can be distinguished in this way. This will provide the possibility to analyze more accurately how transmission chains build up and no longer consider long-term clusters of TB cases in the molecular epidemiology as one cluster, but as separate time-marked transmission chains.
4. A comparison of the clonality of six Beijing genotype isolates from wide-spread areas. On the basis of the observed rate of DNA polymorphism in the six Beijing genotype strains, conclusions can be drawn on how recently the Beijing genotype strains started their worldwide spread. This is highly important in the context of the recurrent tuberculosis epidemic.
5. A comparison of three ‘ancestral’ and three ‘modern’ (emerging) Beijing isolates and thereby insight in the changes in the genome of Beijing strains that may have contributed to their successful worldwide dissemination. This comparison may supply information on the differences in virulence and ability of BCG-vaccine escape between these two groups of strains.

Foreseen follow-up
The whole genome analysis will, after interpretation and publication of the results, be made available to all international researchers working in the field. As only few whole genome sequences are available at the moment this will internationally be highly appreciated. The investigation on the clonality of the Beijing genotype isolates will facilitate new research in the field of the phylogeny of *M. tuberculosis*. Furthermore, the comparison of ‘ancestral’ and ‘modern’ Beijing strains may initiate new research on the pathogenesis of Beijing strains. The analysis of the genomic changes in *M. tuberculosis* strains in long term transmission chains will provide the basis for research on the development of new genetic markers with a fast- and a slow pace of the molecular clock.

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

The immune response to helminth infections shares key features with the allergic response. Remarkably, both the protective and exacerbating effect of helminth infection on allergic diseases have been observed. Although helminth infections have been reported to modulate the outcome of allergic diseases, neither the parasite molecules involved in this immunomodulation have been identified nor are the mechanisms underlying this association (positive and negative) fully understood.

Infections with human helminths affecting mainly individuals in tropical countries such as *Schistosoma sp.* and filaria have been suggested to confer protection against allergic diseases. This however, does not appear to be a universal property of all helminths. Infection with *Toxocara canis* has been associated with the development of allergic diseases in humans. This parasite has a worldwide distribution, including The Netherlands. Helminths are a rich source of glycans (sugars) which are both secreted and present on the surface of these parasites. We are interested in characterizing the effect of these glycan structures both *in vitro* and *in vivo* and to determine their effect in ongoing experimental allergic asthma. To get a better understanding of the mechanisms involved in the negative or positive correlation between allergic asthma and helminth infection, early immune responses have to be investigated in detail. This study will focus on the effect of glycans on antigen presenting cells such as macrophages and dendritic cells and subsequently on T cell stimulation.

**Aim of the project**

Getting a better insight into the mechanisms and molecules involved in the modulation of allergic manifestations in helminth infected individuals is instrumental in our efforts to define molecules able to down-regulate or exacerbate allergic asthma. Focus will be on glycan components since helminths are a rich source of these molecules and because increasing evidence indicates an important role for glycans in immunomodulation. Thus the major aim of the present project is to characterize the effect of helminth glycans on APC maturation, T cell priming and *in vivo* modulation of allergic asthma.

**Strategic and innovative aspects**

Research addressing the role of glycan molecules in immuno-modulation is mostly unexplored within the field of immunology although its importance is increasingly acknowledged. By combining glyco-chemistry with immunology and parasitology, a unique interdisciplinary program is created in the Netherlands that will be internationally highly competitive.

Strategically, the study fits very well in the objective of enlarging immunological knowledge within the RIVM.

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17 This project is related to the project “The effect of *Toxocara canis* infection on allergic asthma using murine models”.

*Infectious Diseases*
Planned activities

This research project will be carried out at the RIVM. Studies will be initiated with experiments *in vitro* and towards the end of the second year *in vivo* studies will be carried out. This research project covers the following three main aspects carried out in the following order:

1. Effect of parasite derived glycans on APC maturation
2. Evaluation of synthesized neo-glycans on APC maturation and T cells stimulation.
3. Evaluation of immunomodulation by glycan pulsed-DC in *vivo*: effect on experimental allergic asthma

Planned products

- Our study will lead to publications in peer reviewed journals in the field of immunology/parasitology/glycobiology.
- Availability of helminth specific glycans that could be used in the development of diagnostics tools for helminth infections. These studies will be the subject for future grant applications.
- The methodology for DC transfer leading to immunomodulation will become available. This method could be used in all kinds of other models with other immunomodulatory molecules.
- “Vital knowledge” at the RIVM. Collaboration with the VU Medical Centre, with the University of Utrecht and AFFSA, Paris, France, will lead to exchange of expert knowledge between academia and the RIVM.

Foreseen follow-up

Results from these studies will contribute to the fields of:

- Immunology, by getting a better insight into the role of glycans in immunomodulation. The role of these molecules is basically unexplored although their role in immunomodulation is acknowledged.
- Parasitology. Glycan molecules are major components of the surface of helminths and are also present in their secreted products. Results from these studies will contribute to our knowledge on the biology of these parasites and on information regarding parasite-host interactions.
- Glycobiology. Studies carry out in this study will provide information on the function of the synthesized neo-glycans.
- Diagnostics. As a spin-off from this project, neo-glycans containing either *Toxocara* or *Trichinella*-specific glycan structures will be available. These neo-glycans can be used for the development/improvement of tools to be used in the diagnosis of diseases caused by infection with these helminths. Diagnosis of toxocariasis and trichinellosis is currently carried out at the RIVM.

The CIb/RIVM will also benefit from this project since the immunological studies carried out in this study fits within the efforts in stimulating and improving immunological research within the CIb/RIVM. This will materialise in the future in the form of publications in peer reviewed journals, additional grant applications, PhD thesis and in the field of diagnostics in SOPs describing new tools for the diagnosis of toxocariasis and trichinellosis both important for humans and veterinary parasitology.
Motivation

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

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

Aim of the project

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

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

Strategic and innovative aspects

The combination of micro-array analysis in murine models of infectious disease with and without vaccine-induced protection, together with genetic studies in well-defined human patient populations, is a powerful multidisciplinary approach to increase our understanding of host-pathogen interaction, host-factors that determine susceptibility to infection, and vaccine-induced protection. Insight into the role of host-factors in host-pathogen interaction in RSV infection is also highly complementary to other ongoing studies into pathogen factors in this process, which are extensively studied by other groups at RIVM. This approach may ultimately lead to the identification of factors that can be targeted to obtain optimal disease-protection, either by vaccination or by therapeutic intervention.

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18 The project is complementary to two other proposals, “Immune pathways in vaccination” (project leader, Rob van Binnendijk) and “Memory immunity” (project leader, Annemarie Buisman)
Planned activities

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

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

Planned products

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

Foreseen follow-up

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

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

Infectious Diseases 46
Motivation

Vaccination strategies aimed at global eradication (e.g. polio) or regional elimination (e.g. measles) are hampered by the continued occurrence or recurrence of small or large outbreaks. Surveillance programs, usually based on the detection of virus-specific serum antibodies, have demonstrated that vaccination-induced immunity is often less robust than infection-induced immunity, and may not be sufficiently maintained throughout life. It is therefore of importance to gain insight into the modes of action of vaccines, more specifically how vaccines enable the induction and maintenance of memory T- and B- cells and the underlying genetic basis of this response. This project will address these issues using a combination of improved virological and immunological techniques and modern genomics techniques to identify the genetic basis of the responses.

Aim of the project

Most of the vaccines currently applied in man, whether inactivated or live-attenuated, fail to induce life-long protection. It is therefore important to establish a rational design in the evaluation of the effectiveness of current vaccines and vaccination strategies. A solid basis for such a design would be to better understand the underlying immunological and immunogenetic pathways mediating vaccine-induced immunity.

Strategic and innovative aspects

So far vaccine-induced immunity has mostly been studied in terms of the induction and persistence of specific antibodies, and more recently also by studying parameters of cellular immunity. However, such an approach will only partially be able to identify correlates of vaccine-induced protection. By implementing novel cellular and immunogenetic techniques (ELISpot, Luminex, microarray) in population-based studies, novel critical parameters of vaccine-induced immunity may be identified. This project will contribute to RIVM's position at the forefront of vaccine knowledge, enabling RIVM to advise on the national immunization program with a sound knowledge basis.

Planned activities

The study will be carried out with peripheral blood lymphocytes obtained from:

1) patients who recovered from acute measles
2) children 14 months of age, before and after their first measles-mumps-rubella (MMR) vaccination
3) healthy adult persons who have received two doses of MMR vaccine

Planned products

- Novel immunological techniques and approaches to measure vaccine-induced protection.

19 This project is related to: SOR project "Memory immunity to vaccine preventable diseases" and "Immune surveillance of vaccine preventable diseases".
• Availability of the micro array technique for the analysis of genes up- or down-regulated in different disease conditions of man.
• Several peer reviewed publications.

Foreseen follow-up
This project will identify new mechanisms and parameters of vaccine-induced immunity. Therewith it will help understanding the complex immune mechanisms following vaccination. It will improve the evaluation of national immunization programs (based on the analysis of serum antibodies), and will promote future studies evaluating vaccine efficacy, as well as vaccine development. The project results are both necessary for RIVM as well as many others in the vaccine field.
Motivation
Ideally, vaccination should provide protection for life by the production of high antibody titers. Unfortunately, both vaccine-induced and naturally-acquired immunity wanes, allowing reinfection to occur. Waning immunity has been proposed to a major cause for the remarkable resurgence of pertussis, which has been observed during last decades in a number of countries including the Netherlands. This makes pertussis one of the major vaccine-preventable diseases today. Waning immunity is currently mostly studied by assessing (decreases in) antibody titers. However, this approach neglects the role of cellular immunity in protection against infectious diseases. A better understanding of the persistence of memory immunity induced by vaccines is likely to lead to a more rationale choice of vaccine formulations and schedules to provide more sustained long-term-protection in the population.

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

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

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

During this project more techniques to identify pathogen-specific memory B-cells in even smaller volumes of human blood will be developed. This will allow us to study memory B-cell and T-cell responses in populations of infants.

This project will explore techniques which can be used to measure cellular immunity to several other pathogens as well. More knowledge about memory immune responses to vaccine-preventable diseases makes it possible to better substantiate the use of modern vaccines and vaccination strategies. Subsequently, we will be able to advise the Ministry of Health whether specific vaccines or booster vaccinations should be given in the susceptible groups identified. Also, the current vaccination schedules can be evaluated more thoroughly.

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[^20]: This project is closely linked to the “Pertussis immunology project”, “Pertussis project”, “Immune surveillance project” and SOR projects “Immune pathways in vaccination”, “genomic analysis of pertussis”, and “Host response to RSV”.

Infectious Diseases
Planned activities

1. Comparison of vaccination with $P_{WCV}$ to $P_{ACV}$ by measuring B-and T-cell memory responses against pertussis and other antigens co-administered with the DTP-IPV-Hib vaccination.
2. Comparison of memory responses of vaccinated individuals with pertussis-infected individuals.

Planned products

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

Foreseen follow-up

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

Project number: S/230436 (C1b.13)
Project leader: Dr. A. J. King (LTR)
Start: 01-01-2007
End: 31-12-2010
Total costs: € 1,125,840

Motivation

Vaccination is one of the most effective methods for the prevention and control of infectious diseases. However, pathogens can impede the efficacy of vaccines by (antigenic) variation and/or changes in the regulation of their genes. This is exemplified by the *Bordetella pertussis* population in which antigenic divergence between vaccine strains and circulating isolates has been documented. The mechanism responsible for this divergence could be recombination of IS elements. This can lead to chromosomal rearrangements that enable *B. pertussis* to quickly adapt to its vaccinated environment. DNA microarrays are powerful tools that allow genomic comparisons between different strains of the same species, such as the comparison of the genomes of unsequenced strains with a sequenced reference strain. We will apply three microarray-based techniques to unravel differences in gene content (CGH), gene order and gene expression in *B. pertussis* strains over a period of 60 years. This study may serve as a model to identify adaptation events in other bacterial pathogens against which the population is vaccinated.

Aim of the project

In this project we will extend the application of microarrays to identify important changes in circulating pathogens that may affect vaccine-efficacy using *B. pertussis* as a model organism. Using the *B. pertussis* microarray, we are able to make genome wide comparisons for many well-defined strains covering the most important periods of the Dutch pertussis vaccination history. In this project we aim:

- To identify changes in circulating *B. pertussis* population on a genomic level: the gene content and gene order.
- To identify changes in circulating *B. pertussis* population on gene expression level: a measure of the RNA and ultimately the protein content.
- To study the relevance of changes identified by microarray analysis in a mouse model.
- To relate the relevant changes observed in a, b and c with changes in pertussis epidemiology.

Strategic and innovative aspects

Microarrays offer a powerful tool for comparative genomics and can therefore be used to study how bacteria adapt to vaccination. Although microarrays have been applied in many research fields, they are still not available for many pathogens. In 2003 the whole genome sequence of one *B. pertussis* strain, the Tohama I strain, became publicly available. We used these sequences to develop the first oligonucleotide *B. pertussis* microarray in the world. We are in a unique position since we have a *B. pertussis* microarray in combination with a well-defined *B. pertussis* strain collection from 1949 up till now, which is present at the RIVM. Nowadays a variety of microarray-based techniques are developed which enable us to utilize the *B. pertussis* microarray not only for the analysis of gene content but also for analyzing gene expression and gene order in these strains. The strength of the microarray technique is that it is easily applicable to a large number of strains.

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21 This project is related to the projects “Molecular Epidemiology and surveillance of pertussis”, “Bacterial Meningitidis”, “Pertussis Immunology”
Planned activities

We will use the unique historical *B. pertussis* strain collection present at the RIVM, comprised of strains isolated from 1949 up till now. The most important periods of the Dutch pertussis vaccination history are: 1. the pre-vaccination period (before 1953), 2. the period in which the vaccine doses was reduced resulting in an epidemic (1976-1984), 3. the period in which pertussis re-emerged 1996-2004 epidemic 4. the period in which the whole cell vaccine was replaced by an acellular vaccine 2005-now. The earlier developed *B. pertussis* microarray will be used to assess the effect of changes in vaccines on the bacterial population, and to identify successful strains (e.g. those causing epidemics). Early identification of epidemic strains may serve as an early warning system in the future. Four main activities are planned:

1. Identification of differences in gene content and gene order in four groups (1-4) of strains
2. Identification of differences in gene expression in four groups (1-4) of strains
3. Study the relevance of differences found by microarray analysis in a mouse model
4. Link differences in pertussis strains to pertussis epidemiology.

Planned products

By analyzing strains over a larger period of time, we expect to gain more insight into the changing genetic profile of successful *B. pertussis* strains in reaction to differences in environmental signals – e.g vaccination. By relating the observed differences to changes in pertussis epidemiology, we will unravel important strategies employed by the pathogen to evade the host immunity. These data will be published in peer-reviewed journals. The project will thus contribute towards a better understanding of this important vaccine preventable disease, which still causes morbidity and mortality, even in developed countries (I). In addition, depending on the outcome, we might be able to define rationales for the composition of future generations of the (acellular) pertussis vaccines (II). The understanding of how *B. pertussis* has adapted itself to vaccination can be applied to other bacterial pathogens against which the population is vaccinated (III). Finally, this project will strengthen the international reputation of the RIVM in the field of vaccine preventable diseases, especially for pertussis (IV).

Foreseen follow-up

The project is expected to provide information and knowledge regarding functional genomics and gene expression profiling of *B.pertussis* to the scientific community. This will improve our understanding of the adaptation strategies, pathogenesis, and evolution of *B.pertussis* in human populations. We expect to identify key genes - important for persistence and resurgence of pertussis - in successful *B.pertussis* strains. Information about the profiles of successful strains will be of great interest for the RIVM and others in vaccine field (for example, vaccine developers) because this knowledge will teach us if the currently used vaccine has a sufficient fit to the currently circulating strains. Thus this project will enable a knowledge-based evaluation of the pertussis vaccine program and may even lead to improved vaccination programs.
B. pertussis Adaptation to Vaccination

Motivation

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

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

Aim of the project

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

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

Strategic and innovative aspects

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

Planned activities

1. **Identification of P3-lineage specific loci.**
   
   Micro-array data have revealed other differences between P1 and P3 strains (A. King, unpublished data). Also, pulsed-field gel electrophoresis typing has confirmed the

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22 related projects are: "Molecular epidemiology and surveillance of pertussis, Bacterial meningitis", "Pertussis immunology", "Identification of B.pertussis escape mutants with micro-arrays", "Host response to RSV and B.pertussis". 

*Infectious Diseases* 53
distinctiveness of the P3 lineage. Therefore, our first aim is to identify additional (potential) adaptations found in the P3-lineage. The complete genome sequence of a pre-epidemic (P1) and epidemic (P3) strain will be determined using a recently developed technology which allows the sequence of a bacterial genome to be completed in 2 weeks at reasonable costs.

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

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

4. Analyses of isogenic strains in the mouse model.
   The experiments described in [3] will be performed with the two strains of which the genome has been sequenced and which are expected to differ at many loci. The individual role of a limited number of P3-lineage specific loci will also be delineated in the mouse model by constructing isogenic strains.

Planned products

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

Foreseen follow-up

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

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

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

Aim of the project

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

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

Strategic and innovative aspects

Quantitative ecological models are recently emerging as decision support tools for the control of health care-associated infections. Key to their predictive validity is the availability of accurate empirical data. In The Netherlands - in contrast to many other countries - these data are available. This poses a unique opportunity for the development of a ‘quantum leap’ research agenda into the dynamics of MRSA, the most important nosocomial and antimicrobial-resistant pathogen at a time when The Netherlands would most decisively benefit from sound advice for future policy decisions.

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23 This project is related to the projects “The impact of healthy ageing on health care use and costs”, “Transmission models in health care”, “Health economics of interventions in AMR”.

Infectious Diseases
Planned activities

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

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

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

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

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

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

Planned products

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

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

Foreseen follow-up

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

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

The increasing threat of an influenza pandemic, the worldwide spread of the SARS epidemic, and fear for a bioterrorist attack with smallpox together emphasize the need to prepare for, detect, and control rapidly spreading infectious diseases. Most activities have been focused on detection of health threats by routine data collection and planning of intervention measures against epidemics of known infections such as SARS and smallpox. Thus far, less effort has been devoted to the characterisation and preparing for control of an epidemic of a novel, unknown disease. The current project addresses this area of investigation by focussing on the development of algorithms to estimate key parameters of an unknown infection once it appears.

Aim of the project

The aim of this project is to develop methods to characterize a newly emerging disease in real time during the early phase of spread. In particular, methods will be developed and evaluated for estimating the following quantities:

• The basic reproductive number of the infection;
• The relative contribution of subgroups to further spread of infection;
• The effectiveness of control measures;
• The optimized allocation of limited supplies to maximize the effectiveness of control.

Strategic and innovative aspects

The proposed project builds on the experience gained by mathematical modelling studies during the foot-and-mouth epidemic in the UK and during the SARS epidemics in 2003. The proposed project adds to this line of investigation by making a link with mathematical modelling studies for optimising interventions, which have up till now presupposed all key transmission parameters to be known. The combination of simultaneous estimation of all epidemic key parameters in the early stages of an epidemic and translating the estimates into suggestions for optimizing control efforts is new and will provide the best possible information during the course of an outbreak of a novel agent.

The RIVM currently has a unique expertise in this area. The proposed project will strengthen this unique position, and will complement the existing work at the RIVM on both syndromic surveillance and writing preparedness plans.

Planned activities

1. Tracking of reproductive number of an unknown infection by developing a method for estimating both the reproductive number and the generation intervals simultaneously.

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24 the project can co-finance the EU projects MODELREL (Co-ordination and dissemination of strategic modelling capabilities to help in public health contingency planning/preparedness/policy for, and mitigation of, the deliberate release of biological agents) and POLYMOD (Improving public health policy in Europe through the modelling and economic evaluation of interventions for the control of infectious diseases) and provides opportunity to collaborate in the U.S. MIDAS (Models of Infectious Disease Agent Study) initiative.
2. Identification of subgroups that contribute most to further spread of infection by extending the developed method for estimating both the reproductive number and the generation intervals to specific subgroups within the population (for example age groups).

3. Tracking of control effectiveness of an unknown infection by using the developed methods for estimating sub-group specific reproductive numbers, and following these over time. We propose to calculate how long it takes after implementing control before one can assess the sufficiency of control measures, and how this depends on the percentage of missing data.

4. Tracking optimized allocation of limited supplies to maximize the effectiveness of control. With the estimated sub-group specific reproduction numbers, generation times and incubation times it is possible to develop a simple simulation model that can be used to explore the consequences of various options for control of the (unknown) infection, when control options are of limited availability.

**Planned products**

Four manuscripts for publication in peer-reviewed journals will be made describing the methods and their application to outbreaks.

**Foreseen follow-up**

Four areas of follow-up have been identified.

- This project will produce a list of essential observables during emerging epidemics of unknown infections which provide the crucial information for public health decision making.

- The algorithms developed in this project will be used, maintained and updated such that they fill the current gap between syndrome surveillance and preparedness plans at the Centre for Infectious Disease Control at the RIVM.

- The methods that have been developed can also be used to well-known infections. There are many assignments by various commissioners that involve assessing an optimized allocation of limited vaccines, or drugs, to achieve a desired public health objective. Having the methods available that are proposed here would give the RIVM a head start in acquiring new projects in this field, for a wide range of well-known infections.

- Another area for follow-up on this project is to use the developed methods to assist local health services (GGD-en) in analysing of local outbreaks of familiar infections.
Motivation
During emerging epidemics of new infections and recurrent outbreaks of familiar diseases, outbreak investigators will go out to collect and analyze information about the cases and their pathogens. Traditional case information like symptom onset date, potential source of infection, age, sex etc. has over the last decades been supplemented, almost routinely, by molecular sequence data (on DNA, RNA or protein level) of the pathogen. The proliferation of sophisticated evolutionary models has placed a burden on researchers to select the model most appropriate for the data, and obscures a glaring omission: there is no model that links the phylogenetic analysis of molecular evolution of pathogens back to an analysis of the epidemic dynamics among cases. Analyses of both the information on cases as well as sequences from these cases will provide about the history of the epidemic. This project will generate a framework for integrating molecular and epidemic approaches.

Aim of the project
We propose to integrate the analysis of traditional and molecular epidemiological data within a single framework. The key idea that enables such a synthesis is to summarize the epidemic as a transmission tree. In such a transmission tree, each case is linked to its infector and to the sequence of the pathogen sampled from that case. In the proposed analysis three questions will addressed:
• How can we best translate observed molecular sequences to ‘genetic’ distances, and observed traditional information on cases to ‘epidemic’ distances?
• How can information from molecular sequence data be combined with information ‘traditional’ epidemiological data?
• Can molecular sequences inform us on transmission routes and dynamics when combined with ‘traditional’ epidemiological data?

Strategic and innovative aspects
The proposed project explores a field of research that is entirely new and uncharted, but borders on two highly active fields of the Centre of Infectious Disease Control at the RIVM: molecular epidemiology and mathematical modelling of infectious diseases. We are not aware of ongoing research in this direction at other research institutes or universities.
We believe that the proposed project will establish expertise in a new and important area that connects two existing highly active fields of research. This will not only extend the existing expertise at RIVM, it will also consolidate RIVM’s unique expertise in using mathematical transmission models for analysis of infectious disease data. This expertise has been essential in acquiring externally funded projects in the past; and hence we are confident that the proposed project will consolidate this capability of acquiring externally funded projects in the future.

25 This project will have strong links with the RIVM projects “Evaluatie Hepatitis B vaccinatiebeleid in Nederland” and “Mycobacteriosen”
Planned activities

Three separate tasks that are required to realise the objectives of the proposed project are defined.

3. Analysis of ‘molecular’ and ‘traditional’ epidemic observations.

Planned products

The major product of the proposed project is the establishment of expertise in the field of epidemic modelling of molecular sequence data. In order to materialize this expertise we plan to write the following manuscripts:

- An overview of approaches to compute ‘genetic’ distances from molecular sequences and ‘epidemic’ distances between cases.
- A technical peer-reviewed paper describing the methodology for combining molecular and epidemic data for inferring transmission trees.
- An applied peer-reviewed paper in a high-impact journal, showing how molecular sequences can inform us on transmission routes and dynamics when combined with ‘traditional’ epidemiological data.

Foreseen follow-up

During this project sufficient expertise in the field of epidemic modelling using molecular data on pathogens will be acquired to obtain external funding for either a continuation of this line of research, or to reformulate our research strategy to merge phylogenetic and epidemic modelling.

Over the last three years, the RIVM’s unique expertise in using mathematical transmission models for analysis of infectious disease data has warranted invitations to collaborate in large international research projects, funded by the European Union or the NIH, as well as new assignments from the ministry of health (VWS). We believe that the proposed project will ensure the RIVM’s unique position, and the associated capability to acquire externally funded projects.
4 Chronic Diseases, Intervention and Lifestyle (CIL)

The significance of chronic diseases is growing, not the least for policymaking at the local and national level. Also from an international point of view, public health issues like chronic diseases and lifestyle are an important research subject. The possibilities of interventions need to gain more attention, because much knowledge is not sufficiently implemented. Specific subgroups of citizens need special attention, or public healthcare. Public health and cure begin to get more intricate relationships; for both areas the responsibility of citizens for healthy behaviour increases. Food, obesity, diabetes, cancer, screening and outcome of care are important topics. Cooperation between sectors already takes place and the interest of this theme will grow and more expertise within RIVM is needed.

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

<table>
<thead>
<tr>
<th>Project number</th>
<th>Title</th>
<th>Author</th>
<th>Costs (€)</th>
</tr>
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<td>Westert</td>
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<td>Hoeymans</td>
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<td>Knowledge Transfer in Public Health</td>
<td>Schuit</td>
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<td>Wijga</td>
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<td>Bemelmans</td>
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**Title:** EUPHIX-2 EU Public Health Information and Knowledge System

**Project number:** S/270106 (V\_Z.01)

**Project leader:** Dr. P.G.N. Kramers (VTB)

**Start:** 01-01-2009

**End:** 31-12-2010

**Total costs:** € 400,000

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**Motivation**

The kind of structured web-based public health information that EUPHIX aims to produce has shown to fulfil an important role in the world of health information in quite a few countries, among which The Netherlands, Norway and Germany. These websites are being consulted by many, including professionals as well as the general public.

**Aim of the project**

The EUPHIX-1 project aims to design, develop and deliver a prototype for a sustainable, structured web-based health information system for the European Union. The system is to provide policy relevant knowledge, information and data on Public Health across the EU, to be integrated in the EU Public Health Portal.

The project has the following key deliverables:

- Structured information content on selected public health issues;
- A functioning prototype for a web application;
- A plan for maintaining the system, using expert networks.

EUPHIX-2 is a second phase for the EUPHIX project for three years. In this phase, a more complete filling and a situation of sustainability by the Commission Services should be realized.

**Strategic and innovative aspects**

The EUPHIX system is unique in focusing on integrated presentation of health data, information and knowledge within a policy relevant context. It should thus contribute to evidence-based policy-making, as well as to health-promoting interventions. The Dutch Kompas is the example for this concept. At the same time, it can be the vehicle for the presentation of data behind the ECHI indicator shortlist, which is a prime goal of health information policy of the EU, and which would acquire a position within the EU public health portal.

A crucial strategic point is the maintenance of the system and its content on the longer term. The prospects are that by 2008 there will be a prototype for the website which is showing most or all of the intended functionalities, but can by no means be 'completely' filled, and also will not be ready to hand over for maintenance to the Commission Services. Therefore, it is anticipated that in the 2007 call for proposals from the EU we will submit a proposal for continuation of EUPHIX into a 2nd phase for the duration of three years.

**Planned activities**

The contract period for EUPHIX-1 is from July 1, 2004 to June 30, 2007. Since the project in fact only started by March 2005, we will formally ask the Commission for an extension period (EUPHIX-2).

By the end of EUPHIX-1, the following products are planned to be accomplished:

1. A functioning prototype;
2. With a consolidated web site environment
3. Including a variety of data for the ECHI indicators (some 30-40), a sizeable number of EuPhacts (some 20), and (some 5-6) EuPhoci
4. A network of experts is available for authoring and reviewing

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26 The project builds on previous work in European Community Health Indicators (ECHI-1 and ECHI-2) projects. EUPHIX builds a lot on the Kompas experience, but also on work in other national web-based health information systems such as the Norwegian Norhealth, and the German GBE.
5. Procedures for further maintenance are set up. If a proposal for EUPHIX-2 would be submitted in spring 2007, contract negotiations may be finished in the spring of 2008. So the duration of EUPHIX-2 could be from 6-2008 to 6-2011.

Planned products

- The main product is a functioning web site prototype and an expert network plus a set of procedures which will enable the EU DG-SANCO to maintain the system after the finalisation of the project. The EUPHIX-1 duration will be too short to realise these goals sufficiently.
- Therefore, it is anticipated that in the 2007 call for proposals from the EU we will submit a proposal for continuation of EUPHIX into a 2nd phase for the duration of three years. In this second phase, a more complete filling and, above all, a situation of sustainability of the system by the Commission Services should be realized.

Foreseen follow-up

Both EU DG-SANCO and RIVM will profit, because this project will result in better comparability of EU-countries in the field of health and healthcare. Furthermore, for RIVM it will be the credits that count, and which may facilitate further contacts and contracts in the future. Once ‘up and running’, the website and its underlying editorial process will provide a comprehensive overview of public health in the EU and its Member States.
Motivation

In Dutch health policy a current research question is 'What is the nature of the interrelationship between healthcare performance and health performance?' The prevailing assumption that publishing a comprehensive battery of indicators will automatically lead to clearer understanding and contextualization of performance may not be tenable. We need to take a closer look at how we actually interpret such indicators in relation to one another, and we have seen that there are no easy rules for understanding possible links between what a community attains in one indicator and what it achieves in another. Since performance is interventionist in nature, health and healthcare performance can be influenced by those who have the ability and resources to do so. Indicators which are correlated with how well certain communities perform in terms of health and healthcare can act as leverage points for improving health.

For the Dutch Zorgbalans the connection with a broader framework must be made in the coming years. The results of this exploratory study serve as a provocative basis for future research into performance interrelationships, that we intend to undertake in the current project. A promising methodology that will be applied in the current project is the Health System Public Sector Value (PSV) model. The PSV model is an analytical framework that governments use to measure their ability to create value for their citizens over time by tracking performance along two dimensions: outcomes and cost effectiveness. We intend to use this model to connect health care performance with health system outcomes.

Aim of the project

The aim of the project is to research the interrelationship between healthcare performance and health performance. The specific objectives are:

- Analyzing the performance interrelationships via rigorously defined international comparisons, in particular, for comparing Canadian and Dutch health system performance approaches and results.
- Exploring, establishing and explaining potential interrelationships across indicators and performance dimensions that signal system performance by using sophisticated analytical techniques and methodologies (e.g. PSV).
- International exchange of knowledge, data and experiences to tackle and contextualize the question of how coherent and balanced performance frameworks can help to improve the performance of health system.

Strategic and innovative aspects

We will be working together with an innovative international group that is ahead of ours. The Dutch and Canadian national health systems are comparable, and Canada has a wealth of data. In early 2006 arrangements were made for collaboration. An interesting way to examine the causal relationships between health and health care performance is to apply Ontario’s Accenture® Public Sector Value (PSV) model to assess and compare the put into operation of health system value creation in each constituency.

A comparative study applying the PSV support tool, reflecting measures of both trend and spatial comparison, could provide useful evidence-based insight towards sustainable development of each health system, thereby examining the causal interrelationships between health and healthcare performance from a truly innovative and functional dimension.

27 The project is closely related to the “ZORGBALANS” within the RIVM, to other projects within RIVM and Canada and will maintain a relationship with the Health Care Quality Indicators Project of the Organization for Economic Cooperation and Development (OECD) in Paris, and the US National Healthcare Quality Report at the Agency for Healthcare Research and Quality (AHRQ) in the United States.
Planned activities

1. To benchmark health system performance in the Netherlands with Canada (Ontario).
   a. Finalize the feasibility study.
      This task is a continuation of a preliminary analysis of the comparability of both countries.
   b. Apply the Public Sector Value method to both countries.
      This task includes
      • Assess data availability in The Netherlands and Ontario in the five year period of 2001-2006.
      • Compile validated performance data from The Netherlands and Ontario.
      • Executive management committees perform weighting of strategic performance dimensions, sub-dimensions, and indicators.
      • Calculate 1) outcomes and 2) cost-effectiveness scores based on Accenture® PSV tool.
      • Identify data gaps and limitations in comparison.
      • Discuss 1) policy lessons from results, and 2) comparative results and benchmarking lessons. Tie in policy and management processes to the results of the PSV analysis to offer evidence-based explanations about both the underlying reasons for, and implications of, outcome and cost effectiveness trends in both constituencies.
      • Organize a strategic committee meeting for both Canadian and Dutch stakeholders.

2. Research the question if PSV is the best tool to tackle the projects main research question
   The second (parallel) task includes a critical analysis of the PSV tool, introduced above, and a review of the literature to refine the tool and describe possible alternative techniques for international comparisons.

Planned products

• Thesis, including 8 international peer reviewed papers.

Foreseen follow-up

The project will help the Zorgbalans- and VTV team to bridge the gap between health care performance and health system performance. It is an important investment in the future of two of the sector V&Z’s central products: VTV and Zorgbalans.
Motivation

With the ageing of the population, more people will have chronic diseases. Although intensive prevention policies can avoid or postpone some of the diseases, in the long run, most elderly will develop one or more chronic illnesses. However, even with chronic diseases, elderly can live active, independent lives. Disease management, health care and the use of assistive devices can diminish the disabilities that come along with diseases. If we are able to reduce disabilities, the gain is not only in a healthier and more active elderly population, but also in reduced demands for long term care, since this type of care is largely determined by disabilities.

Disability is one of the crucial health indicators for the healthy life expectancy, which in its turn is important in the discussion on compression versus expansion of morbidity: is a longer life associated with a healthier life? The Ministry of Health, Welfare and Sport in The Netherlands as well as the European Union made the healthy life expectancy an important indicator to monitor population health.

Aim of the project

The first aim is to determine and describe the trend of disabilities in the Netherlands in the past ten to fifteen years. Although this has been done before it is still not clear what the Dutch trend in disabilities is. Different sources present contradictory results. These differences can be partly explained by differences in questionnaire items, in cut-off points, and in sampling techniques, but it is necessary to bring together the different data-sources we have in the Netherlands to determine the trends associated with different definitions of disability and in different subpopulations.

The second aim is to study and explain the trends in disabling effects of diseases. Do diseases become less disabling? Or in other words: do diseases lead to fewer disabilities now, than they did ten or fifteen years ago? And which diseases are responsible for the major disability in the elderly then and now?

Strategic and innovative aspects

A novelty in this research is that we combine available data sources and methods to describe the trends in disabilities and chronic diseases in the Netherlands. But, more importantly, we will study for the first time the trends in the disabling impact of diseases in the Netherlands. This research is strategic because of the increase in the number of elderly we are about to expect in the Netherlands. This project makes a contribution to the description and clarification of the trend in disabilities which is important for the planning and organization of future health care services. More generally, it is strategic for the RIVM to build on its expertise in the field of healthy ageing. The current project can create, extent or strengthen the (international) network in this field.

Planned activities

1. Determining and describing the disability trend.
   This comprises several steps: getting the data, putting them in a right format, combining the data into one data file, analyzing the data in detail, and meeting with the data-source holders.

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28 Other RIVM-projects under the umbrella ‘healthy ageing’ are related to the current project. There is a close collaboration with several partners (VU University Medical Centre), the Erasmus Medical Centre and the Social and Cultural Planning Office (SCP) in The Hague.
2. Analyzing the relationship between diseases and disabilities. Besides data analyses, a short literature review is part of this process. This review will focus on the explanation of the disability trend, especially on the contribution of (chronic) diseases to disability.

**Planned products**

- Several publications in international peer reviewed public health journals.
- Contribution to the products of the Public Health Status and Forecasts, as the National Public Health Compass and the summary report (VTV-2010).
- Contribution to several European Projects that are waiting for unambiguous information on the Dutch trend in disabilities, e.g. for the OECD (Disability trends and implications on costs of care for elderly populations) and for the EU (EHemu project on Health Expectancy Monitoring).

**Foreseen follow-up**

The findings on trends in disabilities will have its impact on the national health policy as defined by the Ministry of Health, Welfare and Sport. And, if we succeed in finding consensus on the data to use for describing disability trends, also other parties, working in this field (such as the Social and Cultural Planning Office and universities) can benefit from this exercise. Cooperation in these international projects might be one of the benefits from this study. It is our intention to join in with European Research Activities, for example within the EU Seventh Framework Program for Research and Development where ‘Healthy Ageing’ is a cross cutting theme.
Knowledge Transfer in Public Health

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

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

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

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

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

Planned activities
1. Determinants of exchange and use of scientific knowledge:

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29 This project relates to the outcomes of two previous VTV projects. The study will be carried out in collaboration with the VU University, Institute of Health Science, and the Department of Communication of the Faculty of Social Science.
We will make an overview of potential determinants (barriers and success factors) of both knowledge transfer as well as knowledge utilization in practice and policy, by a literature study and focus group interviews. Based on this information a conceptual model will developed and tested among health promotion professionals and policy makers.

2. Demand, supply and use of scientific knowledge

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

3. Development knowledge transfer strategies and evaluation plan

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

4. Evaluation of effectiveness strategies

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

5. Action plan for broader implementation

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

Planned products

- A conceptual model explaining knowledge transfer and -utilization from to practice and policy.
- Contribution to effective strategies to improve knowledge exchange and implementation of effective interventions
- Tailored advice to local health policy makers to obtain knowledge on effective health promotion and support implementation of this knowledge.
- Action plan for broader implementation of effective strategies.
- Five peer reviewed publications in scientific journals and professional and policy journals and a PhD thesis.

Foreseen follow-up

The results of this study can be directly used within the Centre ‘Gezond Leven’ to be established next year within the Division of Public Health and Health Care of the RIVM.
Motivation

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

Aim of the project

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

Strategic and innovative aspects

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

Planned activities

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

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

Planned products

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

Foreseen follow-up

New assignments from VWS will no doubt be acquired when new data on the age range 8-11-14 become available. In addition, we will be able to provide new input for VTV, JGZ, for the Jeugdmonitor and the Chronic Disease Model, based on these data. We also expect that the PIAMA-database will prove to be a valuable source of information on health questions that will come up in the future. We are now providing VWS with important data on the development of overweight in children, although the PIAMA study was originally designed at a time when the obesity epidemic could not yet be foreseen. In the same way, we expect that in the future we will be able to address a variety of lifestyle and health related questions that we cannot yet foresee now. We are confident that, in combination with the data already available, investment in follow-up of the study population with two more rounds of data collection will provide RIVM with an extremely valuable source of data for many years to come.
Title: Chronic Disease in Childhood
Project number: S/260136 (V_Z.06)
Project leader: Dr. A.H. Wijga (PZO)
Start: 01-01-2008
End: 01-07-2009
Total costs: € 212,900

Motivation

Chronic diseases in children seem to receive less attention than the problem deserves (with the exception of obesity). Like we thought until ten years ago, that infectious diseases were a problem of the past, we now seem to think that poor physical health in children is a problem of the past. However, 25% of children and adolescents report at least 1 chronic disease, in particular asthma, chronic respiratory disease, chronic eczema and serious headaches or migraine. We have no systematic insight in the nature, seriousness and prevalence of specific chronic diseases in 0-18-year-olds. Because we expect that the burden of chronic disease in childhood may be more substantial than we currently realize, we propose to systematically assess this question by providing an overview of the data currently available.

Aim of the project

In the study proposed here, the prevalence and consequences of chronic disease in children and adolescents will be investigate. Objectives:

- To provide an overview of the prevalence, types and severity of disease, trends and groups-at-risk for chronic disease in the age group 0-18 years in the Netherlands.
- To provide an overview of the consequences of chronic illness in 0-18-year-olds in the Netherlands in terms of quality of life, social functioning and participation.
- To make our findings available for the practice of early detection, screening and referral in the Youth Health System, for the development and priority setting of the research agenda of the new RIVM Centrum Jeugdgezondheid and for data collection in the Jeugdmonitor.

Strategic and innovative aspects

The project will be a joint effort of the RIVM Centers PZO (Centrum voor Preventie en Zorgonderzoek) and CJG (Centrum Jeugdgezondheid), making optimal use of the experience and expertise available in both Centers.

The project aims to gain insight in the prevalence and consequences of chronic disease in childhood and adolescence and to get an important, but, in our opinion, neglected health issue (back) onto the agenda.

Active sharing and dissemination of the study findings is the main innovative aspect of this proposal. We have always been good at conducting high quality scientific research, but we are only starting to learn how we can make our results reach target audiences in society. We have made dissemination of findings an explicit objective of this project and we expect that future studies and assignments will benefit greatly from the experience we will gain in this project.

Planned activities

1. Two reviews will be produced on the prevalence (1) and consequences (2) of chronic disease in 0-18-year-olds in the Netherlands. These will be based on a literature search of both journals and reports and on consultation of experts and stakeholders. In addition, we will make use of unpublished research.

31 Potential stakeholders are associations of professionals, patients' and consumers' federations and organisations such as VNG, Z-Org and GGD Nederland.
2. Results of the reviews will be actively shared with research institutes, professionals in the Youth Health System and umbrella organisations. An expert meeting will be organised to discuss which of the study findings have the highest priority to be ‘translated’ into practical applications and how this may be achieved.

3. Further dissemination activities will depend on the results that will be obtained and the outcomes of this meeting.

Planned products

- 2 reports
- Paper in international journal or national journal
- Identification of knowledge gaps
- Input for the further development of a ‘signaleringinstrument’ in the Youth Health System
- Input for VTV (Kompas and reports)
- Input for further development of the data collection in the Jeugdmonitor
- Input for policy of the Ministry of VWs
- Input for Youth Health professionals
- Input for the development of the ‘Electronisch Kind Dossier’

Foreseen follow-up

The expected benefits will last beyond the duration of the project. In addition we expect to obtain new assignments from VWS resulting from an increased awareness of the issue and identification of gaps in knowledge and data availability.
Title: Primary Prevention Research on Cardiovascular Diseases and Diabetes

Project number: S/260146 (V_Z.07)
Project leader: Dr. ir. W.M.M. Verschuren (PZO)
Start: 01-07-2007
End: 01-07-2010
Total costs: € 1,100,000

Motivation

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

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

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

Aim of the project

- High-risk approach to prevention of cardiovascular diseases and diabetes: Stratification of the population according to absolute level of risk: optimal targeting of health care resources to subgroups of the population that are at highest risk.

We will examine the sensitivity and specificity of the presently used risk scores for identification of high-risk groups. Furthermore, we will examine whether identification of high risk groups can be improved, by adding risk factors that are simple to measure.

Strategic and innovative aspects

Prevalence of cardiovascular diseases and diabetes is high and will further increase in the near future. CVD and diabetes are responsible for a huge disease burden in the population, and consume about 11% of the total health care budget. Primary prevention is the answer to this epidemic. Two approaches, a population approach and a high-risk approach, complement each other. The present proposal aims to provide necessary information for public health policy. The project will yield important information, tailored to the Dutch situation.

The RIVM has a unique opportunity to profile itself in this field of research.

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This SOR project on cardiovascular diseases and diabetes is linked to the SOR proposal VGC 07, which is aimed at primary prevention research for other chronic diseases (obesity, cancer) and mortality. These two projects together, guarantee a broad scope on chronic disease prevention research. The project has a strong international bedding, we collaborate with 22 other European EPIC centres. Long-term national collaboration, based on several of our population studies, exists with universities of Utrecht, Wageningen, Amsterdam and Maastricht, and with organisations such as the Dutch Heart Foundation (Hartstichting) and Dutch Diabetic Association.
Planned activities

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

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

Planned products

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

Foreseen follow-up

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

Our results facilitate estimation of public health impact through the Chronic Diseases Model of the RIVM and enable RIVM to conduct better balanced cost-effectiveness analyses through better comparing KEAs for primary and secondary prevention (treatment of risk factors).

Although a project duration of 4 years is proposed, by definition harvesting of our large cohorts and related biobanks can go on for another 10-20 years.
Motivation

With the ageing of the population the impact of the ‘old age’ health problems will increase. It is important to gain insight in determinants of health in older age.

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

Aim of the project

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

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

Strategic and innovative aspects

This project is innovative because it combines all relevant aspects of health impact of over- and underweight in the elderly (methodological issues, health care costs and physiological factors). There is paucity of scientific data in this field.

Opportunities for collaboration with cohorts / projects from other European countries will be explored as well as possibilities for additional EU funding (KP7). Besides strategic aspects around the new scientific insights that will be gained, the project is also strategically important because of the obvious opportunities for international collaboration and exposure.

Planned activities

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

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

- Peer reviewed publications
- PhD-thesis

Foreseen follow-up

Both the RIVM and the ministry of Health will benefit from the results. The results can be used for modelling scenarios of health impact (e.g. the Chronic Disease Model), for policy decision making (e.g. assessing priorities in anti-obesity policy measures). They will also provide a basis for further scientific research (e.g. in new round of Doetinchem cohort).
Motivation
Governments need objective information about the health status of their people. Core indicators for describing population health are life expectancy, health expectancy, incidence, prevalence and mortality for a selection of diseases. In most countries data about the occurrence of diseases comes from health interview surveys measuring self-reported disease. Although surveys give a certain picture of the total burden of disease in a population, the observed morbidity is not reviewed by medical experts. It might be advantageous to use also data from registries in general practice (GP) that only count cases which seek medical care and are diagnosed or reviewed by a physician. In the context of the ‘Public Health Status and Forecasts’ (VTV) data of six registries in general practice are used. These register a broad range of diseases, have a long history of registration and cover a considerable practice population. However, incidence and prevalence rates achieved from several registries differ considerably. The researchers could not declare one registry as the most valid one, because all registries have advantages and drawbacks. Neither could they simply clarify this variation. As a consequence the validity and reliability of the Dutch morbidity data, which are to a large extent based on the registries in general practice, is unclear.

Aim of the project
The aim of the project is to increase the quality and usefulness of data from registries in general practice. Specific objectives are:

- Describe the characteristics of the GP-registries and make these public.
- Study the internal validity of the data by comparing the outcomes of the registry with patient records, owed by the GP.
- Study the external validity of the data by comparing the outcomes of the registry with other data-sources, for instance the National Cancer Registry. Knowledge about the external validity should also contribute to improvements in the registration process.
- Extract data of which the validity is known and publish data with and without adjustments for sociodemographic characteristics.

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

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

There will be a collaboration with several universities and other users of data from registries in general practice, like the Dutch Ministry of Public Health, the Centre for Quality of Care Research, the National Association of General Practitioners and the Dutch College of General Practitioners. The current project is related to the projects in the context of the ‘Chronic Disease Model’.
2. Studying the quality of the data, (if necessary) proposing adjustments of the registration process, and computing improved estimates of the incidence and prevalence rates. Also in this study period, estimates of incidence and prevalence rates will be adjusted for demographic characteristics and socio-economic status.

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

**Planned products**

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

**Foreseen follow-up**

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

Project number: S/210116 (V_Z.20)

Project leader: Dr. H.C. Boshuizen (EMI)

Start: 01-01-2007

End: 31-12-2009

Total costs: € 600,000

Motivation

During the last years use of chronic disease modelling has sharply increased, to answer questions from the ministry of health and NGOs, and as part of the Public Health Forecasting documents. The RIVM Chronic Diseases Model (CDM) brings together information a large number of diseases and risk factors (11) in a single integrated model. The DCM integrates this knowledge into a single model together with demographic information. This makes it not only possible to calculate burden of disease indicators (like DALYs) but also to evaluate costs and effects of health policies, to do cost effectiveness studies of interventions and to make “what-if” projections.

This project intends 1) to develop a new implementation of the model, meant for use by researchers at RIVM with some but not extensive training in using the CDM model, 2) to develop a simple version of the model, meant for external use by other EU countries. This part of the project is partially funded by the European Commission.

Aim of the project

The current proposal aims to develop first a new software implementation of the stochastic individual version of the CDM that is flexible and transparent and incorporates state-of-the-art analyses of uncertainty, and second general software tool (DYNAMO-HIA) to estimate the health impact of policies, that is available on the internet.

The specific aims of the project are:

- Develop a modular user-friendly software version of the stochastic version of the CDM,
- Describe the implementation in papers in the scientific literature.
- To build a software tool (DYNAMO-HIA) to estimate the health impact of policies for use by other EU countries and make it available through the internet
- To describe DYNAMO-HIA in a paper in the scientific literature
- To disseminate results by organizing a final conference, including a training seminar.

Strategic and innovative aspects

This research field is innovative, in that nowhere in the world so many diseases and risk factors have been brought together in a single model. This is possible due to the unique position of RIVM as compiler of national disease and risk factor statistics. The project is innovative in that it brings together technological expertise on software development and on scientific modelling. Also new technological developments as distributed computing will be explored, and smart methods for Probabilistic Sensitivity Analysis will have to be developed, as implementation of PSA in models as large as CDM is rare and constitutes a technological challenge.

Planned activities

1. Software development of the stochastic model

The individual stochastic model will be redesigned in a modular form. The overall design consists of the following modules:

- parameter estimation modules

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35 Development of the module for sensitivity analysis will use experience from SOR project S/210106 (Validatie en verbetering van het RIVM Chronische-Ziekten-Model via door sensitiviteitsanalyse gestuurde meta-analyse. RIVM-CDM is also used in other project proposals in SOR (Modelling SES disparities in health, IQA-RUS, Modelling health effects of nutrition). Furthermore, there are external international collaborations with other institutes within the EU project. Main partner in that project is the Institute for Public Health of the Erasmus University.
- population initialization module
- sensitivity analysis module
- micro-simulation module
- result presentation module.

The sequence of development will be decided upon in cooperation with the users of the model.

2. Developing the functional design of DYNAMO-HIA in cooperation with international partners

3. Software development of a DYNAMO-HIA program

**Planned products**

- A software package for chronic disease modelling using that is transparent, can adapt many different types of scenarios, and can be used by relatively inexperienced users
- A description of the program, both in one or more papers to be published in the scientific literature and in a user manual,
- a working prototype of the DYNAMO-HIA model, including a user manual, made available through the internet site
- a paper on the working of DYNAMO-HIA
- a conference including a training seminar on Health Impact Assessment with the model, organized by RIVM

**Foreseen follow-up**

The result of this project will be a CDM that is more flexible than the existing implementation, and which can be used for other types of scenario’s and interventions without the need of further adaptations. The strict modular structure also makes model management easier. Thirdly, redesigning the implementation in a more formal setting, using the software design experience which will be available in the new centre EMI, will increase the transparency of the model. So in the long term RIVM will benefit because modelling and answering questions from the ministry and other parties can take place more efficiently (less adaptation of the software needed), and can be carried out by a larger range of persons (easier planning of personnel).

Being an important partner in the DYNAMO-HIA EU-project will ensure interactions and discussions on modelling with international experts during DYNAMO-HIA meetings, which will increase the quality of work at RIVM, and increase visibility of the RIVM modelling internationally.
Motivation
Health inequalities in the Netherlands are large: those with a lower education have a life expectancy that is 4 year shorter than that of those with a high education. The difference in healthy life expectancy is even 15 years. The Dutch government has formulated as a target that these disparities should be reduced with 25% by the year 2020. Also the European Union has made reducing socioeconomic disparities in health a target.

The RIVM-Chronic Diseases Model (CDM) evaluates the average situation in the Dutch population. Results can not be subdivided by socio-economic group. For the particular case of smoking, a CDM version has been developed to study effects of socio-economic status (SES) on life-expectancy. In order to answer future policy questions on effectiveness of policies to reduce socio-economic disparities, this approach needs to be extended to other life style factors and to diseases.

Aim of the project
The overall aim of this project is to develop methods to model effects of policies on socio-economic disparities in health. Specific objectives are:

- To model SES disparities in life expectancy, disease free life expectancy and DALE (disability adjusted life-expectancy)
- To validate the model by comparing results on disparities to results obtained from observational studies
- To further develop the model by applying it to one of the following questions:
  o Which diseases are mainly responsible for SES disparities in life expectancy and healthy life expectancy?
  o To which extent can disparities in healthy life expectancy be explained by differences in life style factors?
  o What are the consequences of the current trends in obesity and smoking for future disparities in healthy life expectancy?

Strategic and innovative aspects
Socio-economic disparities have become an important research topic during the past 15 years and much information has been collected during this period on socio-economic differentials in health. The project will both contribute to future disease modelling at RIVM (adding an important new aspect by looking at the distribution of health within the population), to future policy making (quantification of effect size makes it possible to see which interventions are most promising), and to science (more insight in effects of using a complex modelling approach compared to the more simple life-table type methods).

Planned activities
1. To agree on the definition of SES to be used in this project. Using educational level is a natural choice, as information on this is available in many data sources, but the feasibility of using additional indicators will be explored.
2. Modelling SES disparities in life expectancy and the effects of life style factors on life expectancy. To model this, data are needed on: SES-specific overall mortality rates or relative risks for SES on overall mortality; SES-specific prevalence rates of life-style related risk fac-

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36 The project is related to the CDM. Several regular projects use this model. CDM is also used in other projects in SOR (“Adaptable Chronic Diseases Model”, “Modelling health effects of nutrition”, IQARUS, DYNAMO-HIA and “Nutrition in our heterogeneous seniors”) as well as of the SOR project S/210106/01. Collaboration partner will be the Department of Public Health of Erasmus Medical Centre.
tors and their transition rates; Prevalence rates of SES. The project will explore how data from different sources (e.g. CBS) can be combined for modelling purposes.

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

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

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

Planned products

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

Foreseen follow-up

The project will result in a version of CDM that enables us to evaluate SES specific interventions/policy and present results of general policy for SES groups specific, and thus enables us to answer future questions of the ministry of health.
Motivation

Economic evaluations as well as so-called impact analyses play an increasing role for the support of policy making. Understandable communication of results is important. Uncertainty analyses often result in a large amount of graphs and numbers. The need to be as outspoken as possible and to communicate in key messages may then conflict with an elaborate presentation of the results of uncertainty analyses. Therefore it is important to develop methods to communicate the uncertainty in the outcomes of economic evaluation in an understandable and concise way to policy makers and others who are interested in the results. Finally, if uncertainties are very large, the important question arises at what point an economic evaluation ceases to be the most useful method and other, maybe more qualitative approaches should be used.

Aim of the project

The aim of this proposal is to develop a feasible and acceptable way to present and communicate uncertainty in (health) economic evaluations that are based on model analyses. The project aims to combine and adjust existing and available knowledge at RIVM, MNP and ErasmusMC. The methods will be developed by using two case studies in the fields of health economic evaluations of public health interventions and/or traffic regulations. Potential case studies are:

- The cost-effectiveness of school programs to prevent smoking in adolescents
- The cost-effectiveness of policies on breastfeeding
- The health impact and maybe cost-effectiveness of a new highway in the AmsterdamAlmere/Schiphol region.

Strategic and innovative aspects

While the MNP has done extensive work in the field of uncertainty analysis and presentation of modelling results, their methods have not yet been applied to economic evaluations. Uncertainty is a crucial element in today's world and its communication to policy makers is a problem. In economic evaluations in health care based on clinical trial data, several methods for uncertainty analysis and presentation exist. However, for evaluations based on modelling, the methodology is less well developed and room for innovation exists.

In the field of economic evaluation in health care, usually uncertainty analysis is rather standard and often limited to a sensitivity analysis. Given the recent attention for uncertainty analysis in economic evaluations an acceptable and more elaborate analysis may currently be regarded as essential to live up to international standards. The project will further improve our position in the field as well as help us to better communicate with policy makers and improve the answers to their assignments.

Planned activities

Semi-structured interviews with policy makers will be set up. Furthermore, the project combines expertise from a number of sources.

1. Extensive knowledge on the analysis and communication of uncertainty developed at MNP

37 The project is complementary to two SOR-projects on uncertainty in risk assessment, namely the project "Identification, Quantitative Assessment and Reduction of Uncertainties in disease burden estimates of environmental Stressors – IQARUS" on environmental health risks and the project "Risk Management by communication about microbial risks" on microbial risks. The project relates to the work in the ongoing SOR project "Validatie en verbetering van het RIVM chronische ziekten model via door sensitiviteitsanalyse gestuurde meta-analyse". Cooperation with the MNP is essential, especially with their experts on uncertainty analysis and communication.
Two points of the guidance for uncertainty assessment and communication (MNP, 2006) ‘mapping and assessment of relevant uncertainties’ and ‘reporting of uncertainty information’ will be relevant for specific approaches for model based economic evaluations.

2. Results from the current SOR project “Validatie en verbetering van het RIVM chronische ziekten model via door sensitiviteitsanalyse gestuurde meta-analyse”. This project aims to develop methods to assess the validity and uncertainty of the outcomes of the RIVM Chronic Disease Model.

3. The current state-of-the-art presentation of uncertainty in cost-effectiveness studies in health care. These evaluations may be distinguished in those closely linked to a single source of primary data (so called trial based evaluations) and those combining secondary data from various sources, often with the help of some form of modelling (model based evaluations).

4. Knowledge on the analysis and presentation of uncertainty in risk assessment modelling at other RIVM-labs (MGB and EMI). In the field of food safety, the economic evaluation part of the CARMA project included an elaborate uncertainty analysis and received widespread international attention because of its innovative character. This information will be used.

5. Knowledge on the analysis and presentation of uncertainty in environmental health impact assessment at MGO. This knowledge will be built up in the SOR project “ICARUS” with the aim to identify, quantitatively assess and reduce uncertainty in environmental health risk estimates. For economic evaluations of environmental policies with an effect on health specific issues are the relations between the intervention and exposure, as well as between exposure and health.

Planned products

- Presentation methods, in the form of two case studies that illustrate a feasible and acceptable way to communicate uncertainty in economic evaluations
- Answer to the question at what degree of uncertainty economic evaluation cease to be useful to policy makers
- Symposium
- Scientific publication

Foreseen follow-up

Results will be of direct use for future (health) economic evaluations performed at the RIVM, e.g. those performed for the Ministry of Health, Welfare, and Sports. The methods developed will help to include uncertainty in a clear way in the key messages of our reports and other products. Furthermore, the project results may support the future integration of uncertainty information in ‘Kompas’.
Motivation

The number of health economic evaluations performed and published increases rapidly and their results are increasingly used in decision making. However, numerous methodological debates lead to variations in guidelines and methods used in different studies. An important area of debate in cost-effectiveness analysis and cost-utility analysis is whether or not to include future health care costs of unrelated medical care. Unrelated medical costs are defined as those costs that solely result from the fact that a successfully treated patient lives longer or that successful prevention leads to prolongation of life. In 2005, as a delivery within the SOR project “Budgetallocatie”, an RIVM report was published that identified the necessity of incorporating future unrelated medical costs in cost-effectiveness analyses. This report also described a methodology to incorporate the costs both of diseases that are causally related and of diseases that are indirectly related to the intervention under study in RIVM cost-effectiveness analyses. It was agreed that the approach was worth further discussion and that ideally, both ratios that include and exclude future unrelated health care costs should be presented in future RIVM research.

Aim of the project

The aim of this SOR proposal is to develop a toolkit facilitating the incorporation of future unrelated health care costs in economic evaluations not using the RIVM-Chronic Disease Model. After development, the toolkit will be applied in two ongoing economic evaluations, namely the evaluation of hepatitis B vaccination for risk groups and the economic evaluation of promotion of breast feeding. These examples are chosen because the interventions involved have effects over the entire lifetime of individuals who receive the intervention, implying that future unrelated medical costs are potentially important.

Strategic and innovative aspects

So far, the vast majority of published cost-effectiveness analyses ignore future unrelated health care costs. While writing the report “Cost-effectiveness analysis with the RIVM Chronic Disease Model (CDM)”, we have discussed our ideas with economists outside the RIVM. Although many colleagues agreed upon the thesis that future unrelated health care costs should be included, practical problems, mainly with regard to data needs, were identified as well. The RIVM is in a unique position to develop a toolkit as proposed because of its access to a large dataset for the “Cost of Illness in the Netherlands” study. This SOR-project involves the development of a toolkit to implement estimations of future unrelated health care costs in economic evaluations that do not use the RIVM-CDM. The toolkit to be developed will be made available outside the RIVM too. This will further enhance visibility of RIVM as an institute of importance within the field of health economics. The availability of this toolkit will improve the comparability of RIVM economic evaluation results because methods are being made more uniform.

Planned activities

1. Identification of the issues that need to be addressed in the toolkit to be developed. A list of questions around future unrelated health care costs needs to be answered.

38 The project is embedded in at least seven other ongoing RIVM projects and builds on the experience and data gathered in the context of these other projects (Cost of Illness; Smoking reducing policies; Prevention of overweight; Budget allocation; Kosten-effectiviteit hepatitis B vaccinatie; Breastfeeding)
2. Development of toolkit + guidance on the use of Cost of Illness data. Systematic description of all issues and choices to be made.
3. Application of toolkit in hepatitis B model and breastfeeding model. Extent current hepatitis B model and breastfeeding model with future unrelated health care costs
4. Reporting on the toolkit

Planned products

- An international scientific paper describing the toolkit in terms of a list of items that needs to be addressed in order to make appropriate choices on the inclusion of future unrelated health care costs.
- All necessary data are or will be made available through Internet.
- Presentation of the toolkit in a workshop.

Foreseen follow-up

Results of the project will be of direct use for all future economic evaluations performed at the RIVM. Besides, the toolkit will also be very relevant for other Dutch evaluation studies, since it provides with guidance on the incorporation of Dutch Cost of Illness data in economic evaluations. The methodology will also be relevant for an international audience, meriting an international scientific publication. The toolkit will contribute to RIVM’s visibility as an institute of importance within public health economics.
Motivation

Performance indicators schemes draw attention to where quality problems may exist in settings where health care is delivered. However, despite large investments in systems for measuring at institutional level, there is still little evidence on the role of performance indicator schemes in health care management and their impact on the quality of care delivered to patients. Limited knowledge is available on how hospitals respond to performance indicators and how measurement actually has been integrated within management and improvement cycles. Furthermore, empirical research has only limited explored the influence of various attributes of performance measurement schemes on the perceived importance. This also goes for values of such schemes and their integration into performance management and quality improvement initiatives in hospitals. Indicators need to be developed according to strict methodological principles and meet certain quality criteria in order to provide valid information about quality of care. This study focuses on the design and application of performance indicator schemes in health care institutions and their effect on professional and institutional performance. It will provide guidance necessary to hospitals and external organisations in designing performance measurement schemes that lead to real improvements in hospital performance. Furthermore, it will assist hospitals and external organisations in understanding in what way health care professionals and management perceive performance measurement and how to improve and create optimal performance environments.

Aim of the project

The overall aim of this study is to explore how performance indicator schemes are designed and applied by external organisations to facilitate institutional performance and the effect of using performance information for external accountability and transparency on professional and institutional performance. Specific objectives are to investigate:

- The importance and value health for care professionals and management in hospitals attach to performance measures.
- Differences in the quality of hospital performance measures between various hospital performance schemes.
- How and to what extent performance measurement and performance management are integrated and applied in performance improvement initiatives in hospitals.
- The relationship between the quality of hospital performance measures and their performance management / improvement initiatives in hospitals.
- The relationship between the performance management / improvement initiatives in hospitals and actual or subsequent hospital performance.

Strategic and innovative aspects

Performance measurement and management in health care has been highly promoted during the past decades and certainly will continue to be high on the political agenda for the next coming

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39 This project relates to two other RIVM-research studies on performance measurement in health care. In this study we will work together with an international project by WHO Regional Office for Europe on performance assessment in European hospitals. The project closely relates to performance measurement and management projects carried out by researcher at the department of Social Medicine, Academic Medical Center, University of Amsterdam.
years. The 2006 Ministry of Health, Welfare and Sports policy agenda has a strong focus on increasing health care quality and safety, in which performance measurement plays an important role. Health care organizations therefore will and need to continue to invest time and resources in the development of such performance systems. This study helps them in the understanding in the design, application and integration of performance measurement systems, in identifying important attributes for making such systems work in practice. This study contributes to RIVM’s future development in the field of performance measurement. During this project there will be a close cooperation with the WHO European project on hospital performance, PATH. This benefit the RIVM and other stakeholders in the Netherlands involved in this field.

Planned activities

1. To investigate what importance and value health care professionals and management in hospitals attach to performance measures. During this period, both a review of the international literature and a survey will be carried out. It mainly addresses issues that related to whether potential users perceive indicators as relevant and of sufficient value, important determinants for action.
2. To investigate differences in the quality of hospital performance measures between various hospital performance schemes. Differences in indicator quality will be assessed using the ‘Appraisal of Indicators Through Research and Evaluation’ (AIRE) Instrument. Analyses include quantitative data analysis, descriptive and inferential statistics.
3. To investigate how and to what extent performance measurement and performance management are integrated and applied in performance improvement initiatives in hospitals. This study involves both a qualitative and quantitative component.
4. Syntheses. In this phase of the project, the associations among those aspects studied earlier in the study (the importance and value health care professionals and management attach to performance measures, the quality of hospital performance measures, and the integration and application of performance measurement and performance management in quality improvement initiatives in hospitals), and between these aspects and actual performance will be studied.

Planned products

The following products/output are/is to be expected:

- PhD-thesis.
- A series (approx. 6-7) of scientific articles published in peer reviewed scientific journals.
- Presentations of study results at national and international conferences.
- Disseminating results via press releases in relevant media or journals.
- An RIVM special issue on indicator development in health care.
- Information / materials to support the Zorgbalans, VTV Public Health Status and Forecast Report, and KiesBeter.nl.

Foreseen follow-up

Output of this study will support RIVM projects such as the VTV Public Health Status and Forecast Report, KiesBeter.nl, the Zorgbalans and IGZ-projects on performance indicators for medical specialists. In all above-mentioned projects performance indicators play a prominent role.
Title: Healthy Ageing & Health Care Expenditure
Project number: S/270166 (V_Z.36)
Project leader: Dr. J.J. Polder (VTV)
Start: 01-01-2007
End: 31-12-2010
Total costs: € 350,000

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

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

• To quantify the influence of health status on health expenditure for citizens of the Netherlands and the Dutch population as a whole, after correction for other expenditure drivers as age, gender, socio-economic position and proximity to death.

• To quantify the influence of co morbidity in relation to healthy ageing and health expenditure.

• To quantify the influence of birth cohorts on health and health expenditure.

• To develop a model for projections of future health expenditure, based on longitudinal and cross-sectional data and using multi-state life-table techniques.

• To develop scenario’s of future health expenditure under different assumptions of ageing and healthy ageing.

Strategic and innovative aspects
This proposal fills a gap in the national and international research agenda. The debate about health expenditures in relation to age and gender is blurred. There are a lot of ‘myths’ about the determinants of health expenditure and how these develop over time. One is the statement that increasing life expectancy will result in higher health expenditure. This research proposal addresses this question by the assessment of the influence of living longer in better (or worse) health. It is the first time that this analysis will be carried out for the Netherlands. As far as we know, even in Europe there has no comparable study been done.

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40The project is related to several SOR-projects (‘Healthy ageing: are diseases becoming less disabling’; Modelling the future of MRSA in the Netherlands; Future unrelated medical costs) and other RIVM-projects.
This project is not only innovative, but has strategic implications as well. The insights can be used in national and international debates on health expenditure. In this sense the proposed study might enhance the position of the RIVM.

Planned activities

1. To quantify the influence of health status on health expenditure for citizens of the Netherlands and the Dutch population as a whole, after correction for other expenditure drivers as age, gender, socio-economic position and proximity to death. This objective will be addressed by cross-sectional analyses.
2. To quantify the influence of co-morbidity in relation to healthy ageing and health expenditure. In the cross-sectional analyses also the role of co-morbidity will be addressed. Information from the patient survey about self-perceived health, number of diseases and physical impairments will be combined with hospital data on diagnoses and health care use. Similar analyses will be done for long-term care.
3. To quantify the influence of birth cohorts on health and health expenditure. Longitudinal analyses of hospital will be performed for different population groups.
4. To develop a model for projections of future health expenditure, based on longitudinal and cross-sectional data and using multi-state life-table techniques. The results of the cross-sectional and longitudinal analyses will be used for the projection of future health expenditure. A simple projection model will be developed using traditional projection technique, as well as life-tables and more sophisticated methods.
5. To develop scenarios of future health expenditure under different assumptions of ageing and healthy ageing. The model will be used to quantify different scenarios of ageing and healthy ageing. We will contrast standard demographic scenarios with more sophisticated. We will distinguish between evidence-based insights and scenarios as developed in other studies and more hypothetic 'what-if’ scenarios.

Planned products

- PhD-thesis.
- A series (6-7) of scientific articles published in peer reviewed scientific journals.
- A simulation model for projections of future health expenditures in different scenarios of (healthy) ageing. A special section on the cost-of-illness website [www.kostenvanziekten.nl; www.costofillness.nl].
- Presentations of study results at national and international conferences.

Foreseen follow-up

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

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

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

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

This project is related to the KP6 projects DIOGENES (impact of diet and genes on weight gain), and INTERACT (genetic and lifestyle factors will be related to type 2 diabetes). Within the current SOR framework this project is also related to projects "Nutrition issues in our heterogeneous seniors" (Nynke de Jong, CVG) and detection of biomarkers through proteomics (Annemiek de Vries, TOX). The project is supported by external grants from EZ/Senter IOP Genomics (IGE03009) and NIH/NIA (PO1 AG17242)
Planned activities

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

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

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

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

Planned products

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

Foreseen follow-up

- Intervention strategies for Dutch population to ameliorate ageing by reducing chronic disease, which will ultimately lead to reduction in health care costs.
- Scientific community will benefit through knowledge on mechanisms on chronic diseases and more in general on the ageing process itself.
- Ministry of Public Health and Sports will be supported on science-based decisions and advice on healthy food policies.
- Integration into new activities at the European level concerning “healthy people”
Title: Primary Prevention Research on Obesity, Cancer and Ageing
Project number: S/350020 (VGC.07)
Project leader: Dr. H. B. Bueno-de-Mesquita (CVG)
Start: 1-1-2007
End: 31-12-2010
Total costs: € 1,200,000

Motivation
The burden of chronic diseases will substantially increase in the near future due to ageing of the Dutch population. The number of cases with cancer, diabetes and obesity will rise. As a consequence it is predicted that around 2015 cancer will overtake CVD as main cause of death. Lifestyle factors play a major role in the development of the most frequent chronic conditions obesity, cardiovascular diseases (CVD), cancer and diabetes, and ultimately in premature death. Primary prevention of these diseases remains the most important way to substantially improve quality of life. Results of this SOR proposal provide necessary input for estimating the possibilities to prevent the major chronic diseases.

Aim of the project
The main aim of the project is to conduct Chronic Disease Primary Prevention Research through better quantifying prospectively the relation between risk factors (lifestyle, including diet and biological risk factors) and the development of chronic diseases, in particular obesity, cancer and healthy ageing, in existing cohorts and biobanks in a national and international context.

Strategic and innovative aspects
The present proposal aims at studying the relations between determinants and disease in several large (inter)national cohorts. The innovative nature of the project lies in producing new and more reliable risk estimates using multi-country cohorts with a large range of exposure and chronic disease morbidity and mortality, and at the same time providing information that is specific for the Netherlands. The international context, wide exposure variation and highly standardized measurements of EPIC (see 'Collaboration') is unique. Also, the Doetinchem Cohort is unique because of the repeated measures over time in the same individuals (4 examinations over a 16 year period) enabling a 'life course approach' to chronic diseases. Unique resources of biological specimen collected prior to clinical diagnosis of disease and frozen at 30°C (PPHV), at -80°C (MORGEN, Doetinchem), and at -196°C (EPIC) enable the discovery of intermediate markers in plausible mechanistic pathways. Through the proposed research RIVM creates a necessary and sufficient knowledge base in chronic disease prevention research in a European context, which also strengthens the RIVM position nationally.

Planned activities
The project will focus on the three topics obesity, cancer and mortality and has strong links with ongoing activities and projects within these topics:
1. Obesity
   a. European nutrient database project
   b. IDAMES

42 This project is linked to a number of ongoing cohort studies and international projects such as EPIC and EU funded projects. The project has strong international bedding; we collaborate with 22 other European EPIC centres. This project is linked to SOR proposal V_Z 7, aimed at primary prevention research for cardiovascular diseases and diabetes. These two projects together, guarantee a broad scope on chronic disease prevention research.
c. Doetinchem Cohort Study
d. EPIC Coordination Action
e. EPIC-PANACEA
f. EPIC-Europe obesity genetics consortium
g. FP7 grant proposal

2. Cancer
   a. EPIC Coordination Action
   b. Colorectal cancer
   c. Pancreatic cancer
   d. Other cancers
   Main focus will be on the role of fruits and vegetables in the etiology of cancer (colorectal, pancreatic).

3. Mortality and ageing
   a. Lifestyle factors and healthy ageing and morality in EPIC
   b. EPIC total mortality workshop
   c. EPIC-Elderly network on ageing and health

Planned products

- Peer-reviewed scientific papers about new and better risk estimates on the role of diet and non-dietary lifestyle factors in the etiology of obesity, cancer, and ageing.

Foreseen follow-up

Published output is expected to play an important role in expert in-/external narrative reviews on the impact of lifestyle factors on the development of chronic diseases, such as done by the RIVM (VTV, PZO), the Health Council, and WCRF. Selected findings on determinants of overweight will be made available through internet (PANACEA). Our results facilitate estimation of public health impact through the Chronic Disease Model of the RIVM and enable RIVM to conduct better balanced cost-effectiveness analyses through better comparing KEAs for primary and secondary prevention (treatment of risk factors), and in some cases (e.g. diabetes) tertiary prevention.

Although a project duration of 4 years is proposed, by definition harvesting of our large cohorts and related biobanks can go on for another 10-20 years.
Motivation

Over the past century, the Dutch diet has become healthier and safer. As a result, general health has improved and life expectancy has increased. However, since only a small number of people indeed meet the Dutch dietary recommendations there is still a health benefit to gain. In order to support policy-makers in assessing the effects of population trends, developments, but also dietary interventions, a method is needed that quantifies any health gains of changes in dietary intake on a population level or on a specific sub-group level. Also this method should be able to quantify any health losses due to specific (unwanted) components in the diet. It is increasingly recognized that the balance between risks and benefits associated with a particular food, food component or total diet should form the ultimate basis for any future nutrition policy. Therefore an integrated risk-benefit analysis is required which converts risks and benefits into a common measure of health impact. Not only nationally but also internationally the need for such approaches exists.

Aim of the project

The aim of this project is to improve current RIVM models, strengthening our position to acquire future research assignments about quantified health effects of food and nutrition. For example, quantification of the confidence limits around the net health impact outcomes would be a leap forward. Moreover another important aim of this project is to work on harmonisation of risk-benefit approaches within the EU (6th EU framework program QALIBRA and BRAFO, and get our RIVM approaches more known and appreciated. The specific objectives of this project are:

- WP A: To extend and fine-tune the currently used method of weighing the risks and benefits of certain food products or dietary components (Risk-Benefit Model):
- WP B: To extend and fine-tune the currently used method to quantify the health effects of certain changes or developments in the population diet (Chronic Disease Model):
- WP C: To investigate the similarities and the differences in model approaches (Chronic diseases model and Risk-benefit model) and outcomes and explore the possibilities for integration based on a case study for fish.

Strategic and innovative aspects

In dietary intervention studies, the follow-up period is usually too short to measure the dietary effects on health. Modelling is a good alternative to simulate the long-term effects. Therefore the innovative nature of the project is a) the fine-tuning of this long-term modelling objective and b) the weighing of benefits and risks, including the involved uncertainties, of foods, dietary components or dietary patterns in a transparent and quantitative way. The project integrates available knowledge from several disciplines into one model, which is unique.

Modelling the health effects of dietary aspects fit in the mission of RIVM to integrate knowledge, conducting risk analysis and projecting implications of policy scenarios. The project will reinforce RIVM’s international position by harmonizing the activities in European projects. This project offers the opportunity to act at fore-front and will put us in a good position to acquire new national and international assignments.

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43 This project is closely linked with the EU FP6 projects Qualibra and Brafo.
Planned activities

1. In WP A, the currently used Risk-Benefit Model will be developed further by:
   A1. Catalogue and prioritize the possible improvements of the risk-benefit model;
   A2. Mapping and quantifying the uncertainties those go along with this model;
   A3. Improve the risk-benefit approach with the help of the case study data;
   A4. Development of the new final framework for integration and outputs of positive and negative health impacts).
2. In WP B the currently used Chronic Diseases Model will be extended and fine-tuned by:
   B1. Prioritize in possible improvements of the Chronic Diseases Model;
   B2. Mapping and quantifying the uncertainties that go along with this model;
   B3. Improve the risk-benefit approach with the help of the case study data.
3. In WP C the similarities and the differences in model approaches and outcomes will be investigated:
   C1. Define a specific scenario for fish;
   C2. Simulate the health impact with the Risk-benefit approach;
   C3. Simulate the health impact with the Chronic Diseases model;
   C4. Improve the approaches for fish;
   C5. Simulate the health impact with the updated approach(es);
   C6. Interpret the differences in the results from the case study;
   C7. To disseminate and profile the methodology and outcomes of the models;

Planned products

- At least four reports on different subjects and two international scientific publications
- Improvements to benefit model in general risk
- Improvement of the Chronic diseases model
- Risk-benefit model for fish
- Updated CDM for fish
- Presentations on international congresses

Foreseen follow-up

The developed methodology can be used to answer future questions of policymakers regarding the health impact of nutrition. For example the models can be used to prioritize the use of resources, i.e. which intervention is most efficient. Moreover, the results attained with our models would be of better quality then the current data and reinforce RIVM’s position to acquire new assignments. Finally, it is anticipated that the more information about the health gain achieved through nutrition becomes available the healthier and safer the European diet might become.
5 Medicines and Functional Foods (MFF)

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

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<tr>
<th>Project number</th>
<th>Title</th>
<th>Author</th>
<th>Costs (€)</th>
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<td>S/370020</td>
<td>MAGIC: Manipulation and Administration of medicines Given to Children</td>
<td>Van Riet-Nales</td>
<td>398,330</td>
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</tbody>
</table>
Motivation

Individual autoimmune diseases are generally perceived as relatively uncommon. Yet, when all autoimmune diseases are combined, the estimated prevalence is considerably higher (3-5%). Autoimmune diseases can be severely incapacitating, underlining their importance to public health. Notable examples of autoimmune diseases include type-1 diabetes mellitus, rheumatoid arthritis, and systemic lupus erythematosus.

Drug-induced autoimmune-like disorders are of a major concern, and as idiosyncratic reactions often reason for withdrawal from the market or restricting their use. Drugs may be easily identified as causative factor in case there is a direct association in time of reactions with the use of the drug, and subsequent improvement after withdrawal.

Aim of the project

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

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

Strategic and innovative aspects

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

Planned activities

1. Assessment of epidemiologic associations of chronic inflammatory autoimmune diseases with drug use. We will investigate epidemiological associations between the long-term use of anti-inflammatory medication using the Doetinchem Study by investigating.
2. Individuals suffering from autoimmune diseases. These will be compared to matched controls with respect to their use of medication.
3. Serum from individuals within the Doetinchem Study for standard autoimmune markers. Serum from these individuals is collected at several time points, it is possi-

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"This project is related to the projects: "Voedseloverigevoeligheid bij kinderen","Gezondheidsbevorderende voedingsmiddelen","Advisering kennisbasis sensibiliserende stoffen", "Specifieke gevoeligheid van kinderen", "Beoordeling van geneesmiddelen"
ble to study the kinetics of alterations of autoimmune markers, and link these to the occurrence of autoimmune diseases.

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

Planned products

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

Foreseen follow-up

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

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

Aim of the project

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

Specific objectives:

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

Strategic and innovative aspects

The innovative nature of this research is the focus on both food and pharma and its interface (functional foods and dietary supplements) and the goal to put the information together and to evaluate (by risk-benefit/effectiveness analysis) them against each other. The database can be used to give information on the interface that neither the Dutch Nutrition Education Centre, the Dutch Consumer Association, the pharmacies, the health promoters themselves nor the food and drug manufacturers do fill at the moment (as they mostly provide information for their particular area of expertise). This project will give the opportunity for

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45 This project builds on previous and current experience with (functional) foods, dietary supplements and drugs within RIVM. Collaboration partners are the University of Utrecht and University of Wageningen.
Planned activities

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

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

Planned products

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

Foreseen follow-up

For the future it is anticipated that both the prototype of the database and the risk-benefit/effectiveness method can be used for new assignments. The usefulness for new assignments is expected to be high, especially for the Ministry of Welfare, Health and Sports, the Dutch Nutrition Centre, the Dutch Consumer Association and also pharmacists and dieticians associations. The database can be used to set up an information platform for consumers and health professionals. The risk-benefit/effectiveness method as proposed can be used as decision support tool to decide which food/pharma interventions can be recommended for a specific population in the treatment/prevention of a disease or enhanced risk factor.
Title: MAGIC: Manipulation and Administration of Medicines Given to Children

Project number: S/370020 (VGC.13)
Project leader: Drs. D.A. van Riet-Nales (KCF)
Start: 01-01-2007
End: 01-08-2010
Total costs: € 398,330

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

Aim of the project
The study aims to improve the health of the children of Europe by scientific research to the ‘Manipulation and Administration of medicines for use in children’. Specific objectives:

• An inventory of the current situation with regard to (critical) quality aspects in the manipulation and administration of medicines for children of 0-12 year age.
• Risk analysis and risk reduction: Within a specified patient group or group of care takers, a risk analysis will be performed of the situation under 1 by relating the frequency of the (critical) quality aspects to the harmfulness of any resulting incompliance for the child and its environment
• Clinical trial: One of the improved formulations, medical devices or patient instructions will be tested in a clinical trial.

Strategic and innovative aspects
The study is meant to explore the field of medicines for use in children, which is currently gaining increased attention from policy makers at a European and national level (VWS) next to health care professionals and Patient Organization Groups. The results allow RIVM to continue to write good quality assessment reports on behalf of MEB (Medicines Evaluation Board) in the Netherlands, also for the expected increased number of applications or variations for medicines for use in children. It therewith contributes to MEB’s strategic business plan to keep its Top 5 position in Europe. The results support RIVM in its task to professionalize the Youth Health Care as it enables RIVM to inform health care professionals on problems related to the administration of medicines for use in children and the associated risk of patient incompliance. This allows professionals to better advice parents or care takers and

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46 The study will be performed in cooperation with the MEB, the UIPS together with the Utrecht Pharmacy Panel for Education and Research (UPPER network) and the UMCU, with special emphasis on the hospital pharmacy and the WKZ. Key experts from the European Medicines Agency (EMEA) will be involved when relevant.
take appropriate action, where necessary. Novel expertise in relation to medicines for use in children may lead to new assignments by VWS, WHO and others.

Planned activities

1. Inventory
   - Literature study
   - Enquiries amongst Dutch children and parents/care takers
   - Interviews patients, pilot enquiry, enquiries, draw up code book and quantificate risks, evaluate risks for the next objective
   - Enquiries amongst health care professionals
   - Interview health care professionals, pilot enquiry, enquiries, draw up code book and quantificate risks evaluate results in the interest of the next objective

2. Risk analysis and risk reduction

3. Product optimization

4. Clinical trial

Planned products

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

Foreseen follow-up

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

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

<table>
<thead>
<tr>
<th>Project number</th>
<th>Title</th>
<th>Author</th>
<th>Costs (€)</th>
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<tr>
<td>S/607001</td>
<td>EIA: Environmental Impact Assessment</td>
<td>Posthuma</td>
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<tr>
<td>S/607002</td>
<td>RCiERA: Research Cooperation in Ecological Risk Assessment</td>
<td>Breure</td>
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<td>S/601001</td>
<td>ITS: Integrated Testing Strategies</td>
<td>Vermeire</td>
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<td>S/630001</td>
<td>Environmental Health; Collaboration IRAS</td>
<td>Lebret</td>
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<td>S/610001</td>
<td>MIRACLE: Modelling Ionizing Radiation and Cancer for low-dose effects</td>
<td>Bijwaard</td>
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<td>S/630002</td>
<td>RAPTES: Risks of Airborne Particles</td>
<td>Cassee</td>
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<td>S/630003</td>
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<td>S/630004</td>
<td>IQARUS: uncertainty in environmental BOD</td>
<td>Knol</td>
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<td>S/630005</td>
<td>PACEHR: Perception, Appraisal, and Communication of Environmental Health Risks</td>
<td>Van Poll</td>
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<td>S/630006</td>
<td>SMARHAGT: SMall ARea Health Analysis: a Geographic Toolkit</td>
<td>Van Wiechen</td>
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<td>S/610002</td>
<td>COURSE: Climate and Ozone Change Effects</td>
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<td>S/680001</td>
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<td>S/680004</td>
<td>Improving Noise Exposure Assessments</td>
<td>Jabben</td>
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Motivation

The project Environmental Impact Assessment, which consists of a number of subprojects, concerns four strategic goals, each of which has a motivation that is summarized below.

1. The research on toxic compounds will fill a strategic gap in a fast expanding field of research: site- or area-specific realistic impact assessment of toxic compound mixtures in realistic multiple stress conditions. This is important related to the development of regulatory lines, like the REACH, the Water Framework Directive and the Soil Strategy.

2. The research on stress effects will fill the strategic gap in a fast expanding field of applied ecology: site- or area-specific realistic impact assessment of man-induced forms of stress on the environment. This is important related to the development of regulatory lines, the Water Framework Directive and the Soil Strategy.

3. Biocontrol Agents (BCA) are increasingly important in crop protection. There is generally no quantitative weighing of the advantages and disadvantages of BCA use versus chemical synthetic crop protection products. Therefore, a tool is needed for this weighing, based on scientific facts.

4. The requirement for post-market monitoring of GMOs (genetic modified organisms) and BCAs has been established under an EU directive. This requirement is based on a public concern that unexpected effects may occur due to large scale cultivation of GM plants and biological control agents, after their release on the EU market. Although the risk assessment considers foreseen effects on the ecosystem, no specialized tools are available for unforeseen ecological effects.

Aim of the project

The aim of the EIA project as a whole is to address the key items that would fill the above-mentioned four gaps, by both scientific research, and thereupon by providing appropriate tools, guidance or other practice-oriented products, as to (1) facilitate implementation of EIA-findings in the respective fields, and (2) pre-sort RIVM as to expected questions posed by primary clients of RIVM in the (near) future.

Specific objectives of EIA are, for the subprojects respectively:

Environmental Impacts / Fundamentals:
The target of this subproject is to extend the classically generic per-compound approaches to ecotoxicological risk assessments for toxic compounds to methods for field-realistic environmental impact assessments, especially:

- The variance in level of protection implicit in the generic quality criteria
- Analysis of patterns in the ecotoxicity data of compounds.
- The eco-epidemiological analysis of monitoring data.
- The results of 'scope-broadening perspective', resulting from RIVM’s participation in EU-NoMiracle
- The results of 'scope-broadening perspective', resulting from RIVM’s participation in EU-ModelKey
• Aggregation of results on site-specific impact assessment, e.g. on the issues of Mode of Action, epidemiology, guidance, mixtures, aspects of space and time in impact assessment, as appropriate.
• Tools for further universal application in the risk and site-specific impact assessment of toxic compounds (e.g. under REACH, WFD or SS)

Environmental Impacts and Sustainability:
The target of this subproject is the filling of an existing scientific-regulatory gap for a successful identification of stability and sustainability in stressed systems. Specific aim is the (mathematical) definition of ecological stability in the framework of BoBI and other terrestrial or aquatic datasets. Objects are:

• Nutrients and allometry.
• Microbial fluxes.
• Ecology, epidemiology and organization of animal populations in human disturbed sites and with mathematical concepts useful in these fields.
• Identification and selection of key features for aboveground ecological damages and selection of the proper parameters for the quantification of belowground effects.
• Aquatic networks
• Density-dependent metabolic scaling
• In addition, two different tools will be provided (Metadata).

BCAs:
The target of this subproject is to establish to what extent the use of BCAs may contribute towards a more sustainable agriculture. Subjects are:

• Differences and similarities between BCAs and chemical pesticides regarding plant health and soil health.
• Development of environmental safety evaluation of BCAs for regulatory purposes. Also, the possibilities of a (semi-) quantitative approach for such an improved tool for the safety evaluation will be investigated.

GMOs:
The target of this subproject is to develop tools and monitor unforeseen GMO- and BCA-induced effects on the soil ecosystem functioning. Subjects are:

• Prerequisites for a national monitoring network for GMOs to study unforeseen effects on the soil microflora, using the already available data and (statistical) methods of the Bobi network as a steppingstone
• Developed tools to monitor GMO and BCA-induced unforeseen effects on soil functioning and results of test in bioassays-1.
• Developed tools to monitor GMO and BCA-induced unforeseen effects on soil functioning and results of test in bioassays-2
• General surveillance of GMOs: monitoring soil functioning under field conditions, results of field studies
• In addition, monitor tools (techniques) and guidance’s will be provided.

Strategic and innovative aspects
The issues touched in the subprojects Fundamentals contributes to the key position of RIVM, with great potential for the future. The models from the subproject Sustainability may inform and improve Dutch and European agricultural policy and water management policies.

It would go too far for this summary to mention all the relations to other projects. Related regular projects are enumerated in the extensive background document to this project, which will be published for use within RIVM as a LER-note.
The subproject BCAs will enhance the quality of the assessment and decision support form the RIVM with respect to potential ecological damage of BCAs.

Strategically, the development of specialized methods and tools for monitoring effects of GMOs and BCAs in the soil ecosystem in Subproject GMOs will address an important public concern. Moreover, the findings can lead to the assignment to implement a national monitoring network as part of the post-market monitoring of ecosystem effects of GMOs and BCAs.

Planned activities

- Environmental Impacts / Fundamentals:
  1. Investigation of level of protection for different species groups.
  2. Screening of existing ecotoxicity data.
  3. Bridging the gap between conceptual risk and factual impact assessment

- Environmental Impacts and Sustainability:
  1. The use of a latent data collection and active building of databases and analysis of riverine and riparian food-webs
  2. Final comparison of model results with currently used qualitative descriptions of "Good Ecological Status" and "Good Ecological Potential". In case of lack of (aquatic) data, focus will remain on terrestrial data and on activities to improve the data situation in the aquatic compartment.

- BCAs:
  1. Investigating differences and similarities between BCAs and chemical pesticides regarding plant health and soil health.
  2. Formulate recommendations for the development of environmental safety evaluation of BCAs for regulatory purposes

- GMOs:
  1. Inventarisation prerequisites
  2. Development of tools-workshop
  3. Testing of tools bioassay
  4. Testing of tools field (after 2010)

Planned products

Numerous products like:

- Tools
- Guidance's
- Peer reviewed scientific manuscripts

Foreseen follow-up

Environmental Impacts / Fundamentals: Activities will be undertaken for internal communication of results, so that the two major tracks (generic risk assessment for setting generic quality standards, and site-specific risk assessment) will be clearly established as 'two sides of one coin'.

Environmental Impacts and Sustainability: This research may give direction to future applied research and improve Dutch and European agricultural (and probably water) policy. This research will also improve further the societal impact of RIVM and its national and international position as expert centre on ecological impacts.

BCAs and GMO's: The comparison of BCAs with chemical pesticides on the aspect of improved soil quality will be of importance in the regulation of pesticides. Such a comparison would lead to a more balanced decision which is in favour of sustainable agriculture. The information provided in this project will therefore be of importance for the OECD and the...
EU. The implementation of the acquired knowledge into the risk assessment is of great importance to risk assessors. There is expected follow-up for RIVM (status as knowledge institute, specifically on BCAs), public (address concern), EU (scientific reasoning for a faster introduction of BCAs on the market without compromising to the safety).

For all subprojects efforts will be undertaken for active dissemination, e.g. during conferences and meetings.
Title: RCIERA: Research Cooperation in Ecological Risk Assessment
Project number: S/607002 (MEV.04)
Project leader: Dr. A.M. Breure (LER)
Start: 01-01-2007
End: 31-12-2010
Total costs: € 773,000

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

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

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

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

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

2. Effect of environmental stress on ecosystem composition and functioning

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

**Planned products**

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

**Foreseen follow-up**

The project will strengthen the position of RIVM in ecological risk assessment and will give it a good position for the realization of commissions in the national and European governments for the implementation of the European Water Framework directive, the European Soil Strategy and regulation of chemicals within the framework of REACH. Furthermore, the cooperation with Radboud University will result in persons educated in the scientific field where RIVM is active and therewith will act as a potential supplier of new well educated staff.
Motivation

Because of the new EU chemicals policy (REACH), ca. 30,000 chemicals have to be assessed within a time-window of eleven years. Current approaches in risk assessment are heavily dependent on experimental animal data, whereas society asks for a high standard of animal welfare. In this view alternative methods for the safety and risk evaluation are urgently needed. New technologies that allow the replacement, reduction and refinement of animal testing are required.

Aim of the project

The aim of the project is to develop Integrated Testing Strategies to be applied under REACH. ITS will make it possible to increase the use of non-testing information for regulatory decision making of chemicals and reduce animal testing without increasing the overall uncertainty. This project contributes to the EU 6th Framework Project OSIRIS (Optimized strategies for risk assessment of industrial chemicals through integration of non-test and test information)

Strategic and innovative aspects

Reducing animal testing is an important political issue in the Netherlands as well as in Europe. The new REACH regulation requires alternative methods. By developing ITS, RIVM will significantly contribute to the overall effort to meet this aim and will strengthen its position as a leading risk assessment centre in Europe. Major innovation concerns the development of ITS embedded in a common decision theory based framework for all (eco)toxicological endpoints.

Planned activities

In this section only the OSIRIS elements with planned contributions from RIVM staff are described. RIVM is not directly involved in testing the output of the project in case studies, but will advise here.

The project is divided in pillars, which are shortly summarized:

1. Chemical domain:
   Developing tools to explore databases with experimental and estimated physico-chemical and (eco)toxicological properties coupled to chemical structure information. This is a basis for further research on effects and exposure elements.

2. Biological domain:
   Developing databases of mammalian toxicological data suitable for modelling purposes and to investigate read-across; creation of a QSAR-based animal-free intelligent testing strategy for ecotoxicology, bases on dividing toxic effects into chemical-specific and species-specific components.

3. Environmental exposure:
   Developing criteria for exposure informed testing, development of refined environmental exposure models and recommendations for modifications of models and

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49 The project further builds on several ongoing projects, such as REACH Implementation Project 3.3 (2005-2006), RIVM SOR ITS (2005-2006), ZonMw QSARs for acute toxicity, OECD QSAR Application Toolbox. The project is linked and contributes to the proposed 6th Framework Project OSIRIS.
tools in current EU-methodology. Improvement of methods for internal and external human exposure assessment.

4. Developing of integration strategies and tools:
Decision theory framework for an ITS that will be used to optimize data, minimize animal testing, costs, time. Logical tools (web tools, probabilistic tools) will be developed.

Planned products
Many products are listed in the proposal. In general they are mentioned below:
- Databases (QSAR, mammalian toxicity endpoints)
- Decision frameworks for ITS
- Exposure and effects modelling techniques
- Tools (data mining tool, web tools for ITS, probabilistic tools)
- Publications

Foreseen follow-up
This project will deliver products which can be used under REACH, starting at one year after the start of the project. Expectations are that this project will lead to further research into integrated testing strategies e.g. within the scope of KP7.
Motivation

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

Aim of the project

The project has two main aims:

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

Strategic and innovative aspects

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

Planned activities

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

1. During the first year, two PhD students will develop specific work plans; start with literature review and preparation of field work.
2. During year 2 and 3 the field work will be executed, and the first results will be analysed and interpreted. After this there will be a mid-term review.
3. During year 4 and 5 the field work will be continued, manuscripts and PhD-thesis will be prepared and the cooperation will be evaluated.

Planned products

- A series of peer reviewed publications

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50 Related SOR-projects are RAPTES, VAMPHIRE, IQARUS and PACEHR. Furthermore, at IRAS, related projects are several PhD-studies, the Academic Collaborative Centre Environmental Medicine project on 'Hospital Admissions and GIS' and the RIVM project SMARHAGT.
Foreseen follow-up

For the two research lines, we anticipate follow-up and add-on activities through the 7th Framework Program of the EU, and application of the developed expertise and know-how in policy support at the national and EU-level.
Motivation
Low levels of ionising radiation are ubiquitous, but accurate and realistic risk estimates are still lacking. For instance, in the Netherlands, where radon concentrations are generally low, each year approximately 800 lung cancer cases can be attributed to radon. However, this number comes with the uncertainty range of 100-1200, which is very large. This uncertainty demonstrates the importance of improving low-dose risk estimates.

Aim of the project
The aim of the project is to obtain better risk estimates for several types of ionising radiation exposures at low levels. A successful cancer modelling approach will serve as a starting point. By fitting the model to exposure data of both humans and animals biologically relevant parameters can be derived and more importantly a dose-response relation can be obtained. From the dose-response relation risk estimates for low-dose exposure can be derived.

Strategic and innovative aspects
Realistic assessment of risks of low-level ionizing radiation is important for common exposures to radon and X-rays, but also in emergency situations such as nuclear accidents. This knowledge is of national as well as international importance and both national and EU collaborations are therefore involved. Risks for several types of cancer, like leukaemia, lung cancer and breast cancer will be determinated.

Planned activities
1. Leukaemia.
   Current animal modelling will serve as a starting point for a leukaemia model of the atomic bomb survivors (available from the Radiation Effects Research Foundation).
2. Lung cancer
   A strategy will be developed how to translate the information on smoking behaviour in case control studies to miner cohorts, and a model will be developed to describe the carcinogenic effects of both smoking and radon exposure.
3. Breast cancer
   A mechanistic model will be developed using frequently exposed tuberculosis patients to describe breast cancer risk due to X-rays in relation to mammography screening.

Planned products
- Methods for more sophisticated estimates of the dose-response relationships of ionising radiation and several important types of cancer
- Knowledge of the important mechanisms involved in radiation carcinogenesis

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51 International collaborations exist mainly in the context of different EU FP6 projects. These contacts as well as new collaborations and research lines are also foreseen to be incorporated in future EU FP7 projects.
• Scientific (peer reviewed) publications
• Contributions to EU and UN reports
• Conference presentations

**Foreseen follow-up**

The knowledge obtained from this project can be used for accurate estimation of effects after nuclear accidents and to inform the public about the risks of common exposures to ionising radiation such as to radon and in medical procedures. The strong position of RIVM in this scientific field adds weight to a likely participation in future EU FP 7 projects. Apart from this, the research facilitates the investigator to fulfil on behalf of RIVM important advisory roles for other EU projects and the United Nations.
**Motivation**

The Clean Air For Europe Program of the European Commission has recently estimated that current exposures to ambient fine particulate air pollution in the 25 EU Member States cause annually about 350,000 premature deaths and a substantial restriction of normal life among tens of millions of subjects with chronic respiratory or cardiovascular disease. However, there is scientific evidence that the mass-based exposure-response relationships of particulate matter may vary in different regions of Europe and locally. This is due to differing exposures from certain emission sources. The future regulation of emissions and ambient air concentrations of particles would greatly benefit from integrated study approaches challenging the whole pathway from emission sources to air quality - human exposure - toxicity mechanisms - health outcomes. More knowledge must be obtained about which specific components are responsible for the observed effects.

**Aim of the project**

The aim of the project is to characterize the physical, chemical and oxidant properties of inhaled particulate matter and establish which of these characteristics are critical determinants of adverse systemic and respiratory effects. In addition, the studies will permit us to determine the mechanisms by which these changes contribute to cardiovascular pathophysiology.

**Strategic and innovative aspects**

The proposed research combines elements from epidemiological and toxicological study designs and will contribute to closing the gap between epidemiological and toxicological findings. Presently little is known about underlying mechanisms responsible for vascular and cardiac effects induced by particulate matter. The innovative potential of the project is that it will not only address the potential adverse effect of PM but will also try to elucidate a mechanism by which they may trigger systemic effects in the body. Another innovation is the use of a Biosampler for collection of size-fractioned particles. Strategic is the close collaboration with the Institute for Risk Assessment Studies (UU).

**Planned activities**

The activities of RAPTES are visualized in a scheme:

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52 The project will be conducted with several national (e.g. IRAS, CARIM) and international partners (King’s College, London; University of Birmingham; University of Edinburgh; University of Umea). The project can provide input to the SOR-project ’Nanotechnology, chances and risk’. It will also provide a perfect base for submitting a future project for EU funding.
**WP1. PM sampling and characterization**
- a) Sampling at various locations with contrast in local source emissions
- b) Physical-chemical characterization
- c) Assessment of oxidative potential

**WP2. In vitro effect assessment**
- a) Plasma and whole blood studies: clot formation, retraction and clot lysis
- b) Endothelial cell studies: modulation of prothrombotic and fibrinolytic properties

**WP3. In vivo effect assessment**
- a) Respiratory tract
- b) Cardiovascular system
  - Acceleration of atherosclerosis
  - Increase of thrombogenicity

**WP4. Field studies**
- a) Human exposure
- b) Animal studies
- c) Physical, chemical characterization & oxidative potential

**WP5. Integration**
- Data analysis
- Interpretation
- Reporting

**WP6. Coordination**
- Controlled human and animal exposure studies performed within BHF funded project will provide baseline information

**Planned products**
The project will provide sufficient scientific information to support three PhD-students in producing their thesis. In addition progress reports and a final report are produced. The results will be presented at (international) scientific meetings and also as short-communication in lay men language. Annual web articles will be prepared.

**Foreseen follow-up**
The output of this project can be used to develop an alternative health indicator to control air pollution with emphasis on particulate matter. It will also contribute to a more source oriented abatement strategy to reduce exposure to particulate matter.
Motivation

For persisting environmental health problems, the societal costs and benefits involved in reducing exposures to acceptable risk levels can be very high. The uncertainty about the risks is typically high, which hampers the appraisal and decision making process. The answer to 'how bad is it?' is quite different to different target groups and users. Therefore there is a great need for more transparent, broad and sound appraisal of societal costs and benefits of complex environmental health problems and environmental policies, both nationally and internationally.

Aim of the project

The overall aim of the project is to develop, test and apply a methodology for integrated assessment of health risk from environmental stressors, in order to support policy in the Netherlands and in the EU. The project sets out to develop and apply a versatile assessment methodology and appraisal framework that allows the evaluation of multifaceted aspects of complex environmental health impacts and risks. An objective is to apply this approach to undertake integrated assessment for different policy areas, in particular on Transport and Household chemicals.

Strategic and innovative aspects

The approach allows for the input and transfer of Dutch practices in a broad European science-policy arena with simultaneous critical confrontation and fusion with approaches adopted abroad. The innovative aspects of the project lie in the broad description of multifaceted aspects of environment health risks and impact, the structured approach to issue framing, the integration across the full chain, different stressors and pathways, in the harmonized application across different policy assessments, the structured incorporation of uncertainty in the appraisal process and the structured involvement of users and stakeholders.

Planned activities

The VAMPHIRE-project is intermeshed in the INTARESE project. As a part of this, VAMPHIRE is instrumental in developing the integration framework for integrated assessments. The scheme below visualizes the process of environmental health impact indicator generation through operational causal chain models; VAMPHIRE will focus on the bottom end of the diagram.

VAMPHIRE acts as an umbrella project and plays an important role in relation to other SOR-projects (IQARUS, PACEHR) and is closely linked to the EU-funded project INTARESE. An important partner project is the cooperation with IRAS (University of Utrecht). Other related projects are: Sustainable traffic, THE PEP, TRANZO, REACH.
Planned products

- Appraisal framework
- Set of protocols and ‘good practice guidelines’
- Toolbox for integrated assessment
- Peer reviewed first author-publications and co-authorships

Foreseen follow-up

The results of VAMPHIRE will benefit national and supranational (EU, WHO) decision making and risk management. The Appraisal Framework may serve the preparation of the next Ministerial Conference on Health and Environment in 2009. Further applications are anticipated through KP 7 projects on environmental health impact assessment.
Motivation

Policy makers, researchers and the general public are increasingly interested in the relative magnitude, severity and rank of environment and health problems. Questions like “Which environmental factors cause the highest disease burden” and “Which policy measure could lead to the largest health gain?” are increasingly being posed to RIVM as well as other (international) institutes. In order to answer such questions, it is necessary to make environmental health problems comparable. Aggregation of environmental health impacts into one single or a few aggregated indicators is greatly needed to summarize, communicate and prioritize these impacts. Such estimates should be comparable, based on sound knowledge, and presented within their proper context, together with underlying assumptions and uncertainties.

Aim of the project

The overarching aim of this project is to identify, quantitatively assess and to deal with or ultimately reduce uncertainties in environmental health risk estimates, in particular for environmental disease burden estimates. More specifically:

- Systematically analyze and describe sources of uncertainty, valuate their relative importance and define good practices to quantify and communicate these uncertainties
- Improve the estimation of duration of environmentally induced health effects, taking into account possible multi-causality, and supported by the introduction of environmental determinants into RIVM’s Chronic Disease Model
- Stimulate further harmonization of quantitative Health Impact Assessment studies

Strategic and innovative aspects

The main innovation will be the explicit consideration of multi-factor causality webs in environmental disease burden estimates and the introduction of environmental stressors in RIVM’s Chronic Disease Model.

Planned activities

Activities planned are:

1. Analysis and description of uncertainties in environmental Burden of Disease estimates: we will select a set of environmental factors to be evaluated with respect to their potential health impacts, based on their policy relevancy and research value. We will organize an expert meeting.
2. Expert elicitation and judgment procedures: we will develop a protocol for expert elicitation and judgments, aimed at making sound and transparent expert judgments for missing values and knowledge in environmental Burden of Disease estimates.

54 This project is related to several SOR-projects. The outcomes of the project will play an important role in the second half of the VAMPHIRE-project and in phase two of the INTARESE project. Furthermore there are relations to several MNP-projects and WHO-projects.
3. Expert consultation – Duration of health effects and multi-causality: we will organize transdisciplinary expert consultations to identify the duration of selected environment-related health effects and to derive scenarios for multi-causality webs.

4. Introduction of environmental factor into RIVM’s Chronic Diseases Model (CDM): we will introduce specific disease categories and input values related to, for example, air pollution and noise into the Chronic Disease Model, which can be used to generate estimates for the duration of (environment related) health impacts. Comparisons will be made with the public health impacts of certain lifestyle factors, using similar outcome measures.

5. Identification, Quantitative Assessment and Reduction of Uncertainties in disease burden estimates of environmental stressors: elements of all parts of the project will be used to give an overview of main uncertainties in environmental Burden of Disease estimates, including best practices to manage and communicate these uncertainties.

Planned products

- Protocol to introduce environmental factors into the CDM
- Protocol for environmental Burden of Disease expert judgments
- Several peer reviewed scientific publications

Foreseen follow-up

Methods and tools can be used for further Health Impact Assessment work and policy support or evaluation. The project may well lead to new assignments, for instance in the EU 7th Framework Program. Cooperation with WHO will be strengthened.
Motivation

The Appraisal Framework Health and Environment is a tool for a broad and systematic description of the knowledge and scientific evidence on environmental health problems. It allows for even-handed treatment of environmental health problems based on standardized description of the problems. In its current form, the Appraisal Framework is a questionnaire-based checklist with 26 questions, addressing five key issues relevant for environmental health problems (extent and severity health effects, perception, interventions, and cost and benefits). One of the experiences with the Appraisal Framework is that some of the issues are treated rather qualitatively, in particular the psychometric aspects, that determine risk perception and acceptability. There is substantial empirical evidence in the literature on their importance in the perception of risk. An obvious question is how to describe these aspects more systematically and preferably quantitatively when evaluating or comparing complex risk problems. The Dutch Health Council reviewed the Appraisal Framework and recommended the use of multicriteria analysis and other techniques and instruments from decision analysis and policy analysis to further develop the Framework.

Aim of the project

The main aim of this project is to facilitate the deliberation process on environmental health risks with relevant risk information, tools and guidelines. More specific aims are to:

- Assess stakeholders' perception of several environmental health risks
- Design an appraisal framework for deliberations on environmental health risks
- Setting up risk communication strategies for environmental health risk
- To provide a guide book to support deliberations and environmental risk for various stakeholders.

Strategic and innovative aspects

The innovative nature of the project lies in the fact that we aim at furthering Multi Attribute Utility Theory/Multi Criteria Analysis (MAUT/MAC) as tools for RIVM risk assessments in the environmental health domain. Until now, the application of these methods in the environmental health domain is limited. Development of knowledge and skills in risk perception and decision-support is essential for RIVM to keep up with future information needs for regular commissioners (e.g. VROM and VWS) on risk perception, appraisal and communication. It is also important to develop this type of expertise to preserve a front-runner position in the field of risk assessment, at a national and international level.

Planned activities

The project comprises 4 distinct activities:

1. Perception
   - Systematic quantification of stakeholders’ perceptions on several selected risks. Respondents will be selected from up to 14 European countries. From psychometric risk

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Collaboration is readily established through collaboration with partners in the EU KP7 project 'INTARESE', in which RIVM already participates. Academic collaboration is established with several Universities and the EMGO-institute for Research in Extramural Medicine.
research (Psychometric Risk Paradigm) relevant risks aspects will be selected. MAUT/MCA will serve as a methodological framework.

2. Appraisal
   With the application of techniques and models form MAUT/MCA the previously developed ‘Appraisal Framework Health and Environment’ will be elaborated. Each of 8 stakeholder groups will participate in 4 or 5 group sessions. The result will be an evaluation procedure for environmental risks extending the Appraisal Framework on two aspects: weighing relevant risk aspects and aggregating single-aspect utilities into overall utilities for risk comparison purposes.

3. Communication
   Information and communication needs for different stakeholders on different risks will be assessed in focus group discussions and structured interviews, guided by the ‘Sender-Message-Receiver’ concept. The results will be used to develop and improve risk communication strategies.

4. Synthesis
   Synthesis of knowledge and skills from the aforementioned activities into a ‘green book’ on risk perception, appraisal and communication as a ‘helping-hand’ for decision-makers.

Planned products

Deliverables are:
- European database on perception of environmental health risks
- Conference presentations
- 3 peer-reviewed journal articles
- Greenbook on Risk perception, Appraisal and Communication

Foreseen follow-up

Follow-up is foreseen along two lines:
- The procedures and tools developed in this project may be successfully used for the analysis and deliberation on other than the selected environmental health risk. This may be even used on risk in other domains than the environmental health domain.
- A cognitive approach of risk perception is adopted. In nowadays developments in risk perception research risk perception is seen as a dual process, a mixture of feelings, intuition and cognition. In the future risk assessments comprising risk perception the approach presented in our proposal may be extended by the dual processing approach.
Title: SMARHAGT: SMall ARea Health Analyses: a Geographic Toolkit

Project number: S/630006 (MEV.20)
Project leader: Drs. C.M.A.G. van Wiechen (MGO)
Start: 01-10-2007
End: 01-04-2010
Total costs: € 599,340

Motivation

The environment plays an important role in human development and health. When public interest in the actual health consequences of environmental risk factors at the local level increases, members of the public are likely to notice unusual aggregations of disease in a small neighbourhood and attribute it to a nearby source of pollution. To investigate these claims, it is essential to have access to reliable disease incidence or prevalence data in a given area, and relate the number of observed cases to the number expected for a comparable reference population.

Aim of the project

Aim is to develop a toolkit facilitating environmental health research with routine health data in small geographic areas including a protocol describing the decision making pathway for using the toolkit. Specific objectives:

- Facilitating rapid disease mapping using RIF (Rapid Inquiry Facility) to explore possible links between environmental exposure and health outcomes.
- Facilitating more advanced geographic correlation studies with space-time modelling increasing the power of results.
- Facilitating specific cluster methodologies to detect spatial or space-time disease clusters.
- Building national databases with geo-coded environmental exposures and demographic and socioeconomic indicators for use at small area scale.

Strategic and innovative aspects

Methods will be developed and implemented to bridge the gap between health surveillance and environmental monitoring. With the tools, we will be able to adequately respond to environmental health questions from the public, policy and political domain. Ecological studies analyze data at a group level but aim to make inferences about the individuals within the groups. Although ecological studies have various advantages, ecological inference is often subject to bias. Recent methods are developed to reduce such problems, for example by adding small samples of individual level data to the ecological level. The benefits and usefulness of such partial ecological studies will be explored in this study and implemented in the toolkit if feasible.

Planned activities

Activities are:

1. Disease mapping tool
   Implementing the RIF, carrying out pilot study.
2. Geographic correlation tool
   Improving methodology, developing user friendly tools in statistical software, carrying out pilot studies.
3. Cluster analysis tool

SMARHAGT is related to SOR-projects ‘Improving noise exposure assessments’ and ‘Rapid assessments after disasters’. An international project that is related to SMARHAGT is EUROHEIS-2.
Implementing cluster analysis methods, carrying out pilot studies.
4. Databases on exposure, population and confounders
   Collecting yearly data, processing and converting data to small area scale, building database.
5. Improving ecological inference
   Implementing methodology, preparing survey data, carrying out data analyses.
6. Protocol
   Writing en testing
7. Workshop

Planned products

- Disease mapping tool with factsheet
- Geographic correlation tool with factsheet
- Cluster analysis tool with factsheet
- Database on exposure
- Database on population and confounders
- Protocol
- Several scientific papers (base of a PhD-thesis) and a workshop

Foreseen follow-up

SMARHAGT can lead to new assignments by national or regional commissioners who are responsible for surveillance and identification of environmental health risks.
The tools produced by SMARHAGT will be essential in the back office of the ‘Expertise Platform for Health and Environmental Monitoring’, as proposed by the Health Council of the Netherlands in 2003, and supported by the Ministries for VWS and VROM in 2005.
Title: COURSE: Climate and Ozone Change Effects

Project number: S/610002 (MEV.23)
Project leader: Dr. H. Slaper (LSO)
Start: 01-01-2007
End: 31-12-2010
Total costs: € 805,000

Motivation
Climate and ozone changes are among the major global environmental threats, and both can have important implications for the solar UV-radiation received at the ground. Solar UV-radiation has a wide variety of effects on human health, air quality, aquatic and terrestrial ecosystems and food chains. UV-exposure is regarded as the main causal factor in the etiology of skin cancer, with more than 20000 new cases and around 500 deaths occurring in the Netherlands each year. Furthermore, UV-exposure contributes to the formation of cataracts and thus to the 80000-90000 cataract operations that are performed each year in the Netherlands. On the other hand, low UV-exposure in certain groups can lead to a deficiency in vitamin D production in the skin; with consequences for bone-formation and possibly vitamin D deficiency also contributes to a higher incidence of several internal cancers in certain risk groups.

Aim of the project
• To improve, integrate and further validate new satellite and ground based approaches for the assessment of the past and present UV-radiation levels in relation to atmospheric change, and
• To improve the methods for the scenario analysis of future developments in UV-radiation levels and health risks in relation to past and future environmental changes.

Strategic and innovative aspects
The project will lead to a considerable innovation of the Assessment Model for Ultraviolet radiation and Risks (AMOUR), which has been widely applied in (inter)national environmental assessments to analyze future developments and risks related to changes in the biologically relevant UV-climate. A major limitation of the present model is that it primarily treats the ozone changes independent from the climate changes. The AMOUR-model will be considerably improved by integrating modelling results from runs with coupled climate chemistry models, which will become available from the European SCOUT-project, and by including results obtained from the UV-climatology assessments and UV-measurements. These substantial improvements of the risk assessment methodology will strengthen RIVM’s current position as an integrator of knowledge on the full source risk chain for ozone and climate change effects on UV-radiation and risks, and thus for two persistent and major global environmental issues. Furthermore, the project will enable RIVM to strengthen the international collaborations with leading institutes and researchers in ozone-UV and climate research.

Planned activities
The main activities of the project are divided in three closely connected work packages:

\[57\] The project is closely connected to international collaborations, such as the EU FP6 integrated project SCOUT, the COST-726 action on analyzing the past UV-climate in Europe. Close collaborations has been established with a large number of leading international research groups, among which universities of Hannover, Thessaloniki, Finish Meteorological Institute, BOKU University Vienna.
1. Validation, improvement and analysis of satellite retrieval methods to estimate the UV-climatology, focusing on the newly available platforms, such as OMI, and data-continuity to establish long term changes and trends

2. Ground based spectral UV-measurements at CESAR-site, data-quality assurance and the analysis of the biologically relevant UV-climate and variations and trends therein (using data from the European UV-database obtained from SCOUT-project and COST-726 actions)

3. Improvement of the AMOUR-assessment model by integrating results from coupled climate chemistry models, expanding geographical area, effect coverage

**Planned products**

Products are:

- Analysis of the European UV-climate. Reports and publications on the validation of methods for the assessments of the past and present UV-radiation levels at the ground, combining and validating new satellite based instruments and approaches with high quality spectral UV-measurements and modelling approaches using ground based ancillary data.
- Papers on quality assurance and quality control techniques of spectral UV-monitoring systems, and on the influence of temperature of the input optics on the irradiance calibration.
- Operational and fully update version of the AMOUR-model and update analysis of skin cancer and cataract risks to ozone depletion and climate change.
- Several peer reviewed publications on these topics.

**Foreseen follow-up**

Results of the project will lead to collaborative scientific publications and through improvement of the existing risk-assessment models to contributions to future environmental assessments.
**Motivation**

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

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

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

**Aim of the project**

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

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

**Strategic and innovative aspects**

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

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58 The project is related to several monitoring networks in the Netherlands and to DOAS (Differential Optical Absorption Spectrometry).
Planned activities

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

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

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

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

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

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

Planned products

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

Foreseen follow-up

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

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

Aim of the project

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

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

Strategic and innovative aspects

The importance of the comprehensive research station CESAR is widely recognized. Development of the site as a central node in international networks is important. The project will provide gap-filling knowledge on atmospheric profiling to reduce uncertainties in the understanding of climate change. A Raman lidar will be developed, necessary as a key-instrument. New techniques will be developed, demonstrated and validated.

Planned activities

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

59 The project is related to national and international projects on climate, aerosols/particulate matter and air quality, e.g. EARLINET-ASOS, SatLink, AeroPro, EUSAAR, AQURES (SOR-project) and RAPTES (SOR-project).
regions, including the US and Asia, are expected and will be supported through this project.

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

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

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

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

Planned products

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

Foreseen follow-up

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

Diagnosis of air quality over Europe is currently based on a patchwork of ground-based national and regional monitoring networks. Data from these networks is not available in a single database in real-time. Prognosis of air quality is largely based on statistical models using a limited number of meteorological parameters. Substantial progress in this diagnosis and prognosis can be made by integrating the existing ground-based monitoring infrastructure, new monitoring instruments in space and advanced modelling.

Aim of the project

This project aims to gather and effectively combine air quality measurements from satellites and ground-based monitoring networks in Europe. All measurements will be ingested and integrated in a state of the art assimilation model. The resulting instrumentation will allow diagnosis and prognosis of air quality over Europe with unprecedented accuracy, spatial coverage, and spatial and temporal resolution. Running in real-time mode this new instrumentation will also provide more accurate and more detailed smog episode forecasts.

Strategic and innovative aspects

The research aims to achieve a number of goals that have not been achieved before: the validation and use of new satellite data of air quality in the lower troposphere, the real time availability of European ground based network data, and the integration through data assimilation techniques in air quality modelling.

The proposed research is strategic because it facilitates setting up a national collaboration in the Netherlands with the key partners in the field, that will also internationally be considered powerful and an attractive collaboration partner. This will open up many opportunities for international collaboration and co-funding. It positions the Netherlands and RIVM in the heart of important European and international programs GMES and GEO. It is expected to bring the next important step forward in two RIVM core tasks: the diagnosis and prognosis of air quality.

Planned activities

1. SMOGPROG: towards operational smog forecasts using NRT satellite measurements
   SMOGPROG will integrate the Dutch monitoring network LML, the CESAR observatory in Cabauw, space based observations and modelling to produce a more accurate smog forecast for the Netherlands.

2. RSVP: validating satellite measurements of trace gases
   RSVP is a satellite validation project aiming to set up in the Netherlands the ground-based instrumentation necessary to properly validate the satellite observations of ozone and NO₂, and to use it in a number of validation studies.

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60 This project is related to several external projects, co-funded by NIVR as part of the User Support Program and to the SOR-project CESAR. There are many collaborating partners in Europe, e.g. The LOFAR consortium, European Commission (EC), European Environmental Agency (EEA), European Space Agency (ESA), National Aeronautics and Space Administration (NASA), European Centre for Medium-Range Weather Forecasts (ECMWF).
3. **LOFAR-AQ: towards a real-time European groundbased network for air quality monitoring**

Integration of European groundbased air quality monitoring networks, making the measurement results from these networks available in real time in a single database.

**Planned products**

- An integrated network of real time groundbased observations of air quality on the European scale.
- Validated air quality measurements from space for nitrogen dioxide and ozone, available in real time.
- A model system that will integrate information on: air quality observations both from groundbased networks and from space, emissions of air polluting substances, and meteorological conditions and developments.
- High quality detailed 4-D maps of air quality over Europe that can be used for forecasts and many diagnostic studies much like is done for the weather in today's Meteorology.
- Web based communication tools to make this information accessible to stakeholder specialists and the general public.
- A substantial number of peer reviewed scientific publications and conference presentations/posters and A PhD.

**Foreseen follow-up**

Results of this project will be used both inside and outside RIVM. Once the project has been completed, further assignments are foreseen from the ministry of Environment (VROM), the Netherlands Environmental Assessment Agency (MNP), the European Environmental Agency (EEA), the European Union (EU) and the European Space Agency (ESA). The general public will benefit from it through the availability of high resolution air quality maps and a “chemical weather forecast” on internet.
Title: Improving Noise Exposure Assessments

Project number: S/680004 (MEV.28)

Project leader: Ir. J. Jabben (LVM)

Start: 01-01-2007

End: 31-12-2008

Total costs: € 450,000

Motivation

Research indicates that high noise loads from transport activities, e.g. roadways, airports and railways, not only causes annoyance but also disturb sleep quality and, in the long term can even cause health effects such as high blood pressure and cardiovascular effects. Continuous development of the knowledge of various types of noise exposure and deepening the understanding of the relation between noise exposure and effects are necessary. In particular, the present knowledge of the influence of time and spectral characteristic of noise on human perception should be improved.

Aim of the project

The focus is to obtain a more complete picture of noise exposure in the Netherlands than currently available, not only including average noise levels, but also including (low frequency) character, maximum noise levels and background noise levels. The results will thus allow a better understanding of the relation between noise exposure and human perception and better predictions of the effects of new traffic developments and noise measures. The results will be widely of use within RIVM both for Noise Monitoring and Health Impact Assessment purposes.

Strategic and innovative aspects

The project will help RIVM researchers to obtain a broader view of noise issues and enable them to offer policy makers better and more adequate information for effective combat of noise exposure and its detrimental effects on human health and society. The project is innovative as for the envisaged broadened and refined knowledge of the noise exposure. Using additional information on temporal variation and statistical distributions of traffic volumes, it will become possible to gain insight into maximum noise levels and background noise levels. This may contribute to a better match between noise complaints and annoyance and the actual noise exposure.

From a scientific point of view, the project will contribute to the knowledge of frequency dependent sound propagation under various meteorological conditions. There is relatively little, well documented material available about variations, maximum noise levels and low frequency noise. It is expected that this project can yield important innovative contributions. In particular, during the first half of 2008 a large series of outdoor noise measurements will be performed under different meteorological conditions.

Planned activities

1. Innovating and broadening noise mapping methods: temporal aspects and frequency aspects
   The current mapping tools will be extended with new methods, to be able to deliver the envisaged noise indicators.

2. Validation of noise mapping methods
   The tools developed (noise models) will be validated, by using the results from the noise monitoring network of RIVM. Insight in the range of validity and uncertainties will be gained.

61 The results of the project are also beneficial to the SOR-project (SMARHAGT)
3. Investigating noise exposure versus human perception
The obtained noise exposure will be combined with spatial data concerning health effect, noise complaints and annoyance. In particular it will be investigated whether the extended noise maps can contribute to better correlation between noise exposure and human perception.

Planned products
- A set of improved and extended noise maps.
- Four papers to be presented at international conferences.

Foreseen follow-up
The project will be beneficial to both policymakers and public as it will enable RIVM to provide them with more adequate information regarding questions on environmental noise pollution and its effects. The tools developed in this project and resulting database will contribute to the quality and importance of future RIVM noise studies carried out on both National and International level.
On a national level, the results will be of interest for the Dutch ministries of housing and spatial planning and of Transport Public Works and Water management for evaluating the health impact of new infrastructure and for validating and optimizing their noise policies. Results could also be of use for county councils and municipals, as the European directive obliges them to provide the public with information concerning noise exposure. Potentially RIVM could play a role in this process.
Title: **Chlamydia positivity and prevalence**

**Project number:** S/210056

**Project leader:** Mirjam Kretzschmar (CIb – EPI)

**Start:** 1-7-2008

**End:** 30-6-2010

**Total costs:** €195.000 (2008-2010)

**Motivation**

There is an urgent need to develop robust and efficient methods to monitor the success of population screening programs for genital *Chlamydia trachomatis* (CT) infection in reducing population prevalence. The start of a large scale pilot screening program for chlamydia in three regions of the Netherlands (Chlamydia Screening Implementation (CSI)) provides a unique opportunity to do this. First evidence from the English National Chlamydia Screening Programme (NCSP) that started in 2003 shows that positivity measured in population screening may actually be considerably higher than prevalence measured in an independent prevalence study. However, these studies were cross-sectional and did not consider factors associated with the chance of being screened and the risk of infection. This project aims at elucidating the relationship between the fraction of positive tests observed during a population screening program conducted over a longer time period and the prevalence in the target population.

**Aim of the project**

In the study proposed here we want to unravel the various factors that determine the relationship between positivity and prevalence by drawing together empirical data from various sources and combining it with a modeling study.

**Strategic and innovative aspects**

The proposed study combines a number of innovative approaches. It uses data from a large scale CT screening project that is set up specifically to supply information about changes in population prevalence based on a stepped-wedge study. This unique data set will be combined with a state of the art mathematical modeling approach to describe the transmission dynamics of Chlamydia.

There is an ongoing debate in the scientific world regarding the explanation of increased notifications of Chlamydia. Therefore the results of this research are of importance not only for the CT screening policy in the Netherlands, but will contribute substantially to the understanding of the effects of screening on Chlamydia prevalence in other parts of the world.

**Planned activities**

The project can be divided in the following steps:

- **Inventory of data sources to look at relationship between positivity and prevalence:**
- **Collection of additional sexual behaviour data about people being tested for chlamydia, and chlamydia testing practices in health care settings.**
- **Use results from CT screening pilot as a reference point for the prescreening situation. It will serve as input for model validation.**
- **Use simulation model to look at various screening scenarios and their effect on positivity and prevalence.**

Related projects: Chlamydia-screening (PILOT CT) project; Chlamydia Screening Implementation (CSI) project; various international collaborations.
• Implement acquired immunity in the model and explore effects. Aim of this part of the study is to gain understanding of how immunity could impact on incidence if large scale screening is introduced.
• Using the model we will compare prevalence and positivity rates for various screening scenarios: The result will be an assessment of how to interpret CT positivity in terms of population prevalence of C. trachomatis.
• Writing of publications for international peer-reviewed journals.

Planned products
Foremost the project will provide an understanding of how various factors influence and determine the quantitative relationship between CT positivity and prevalence, and how this impacts the validity of using positivity measures to estimate Chlamydia prevalence in the course of long term population screening for Chlamydia infections. From these insights we will obtain:

• Information on what additional information is needed to obtain reliable prevalence estimates from positivity measures
• Conclusions for a more effective design of a screening program (e.g. with respect to screening intervals, re-screening policy for those tested positive, efforts necessary for partner notification and treatment)
• Reliable prevalence estimates can then be used for estimating the burden of disease for Chlamydia and for cost-effectiveness analysis of intervention measures.

Finally, we think that the methodology and conclusions developed in this project can also benefit the evaluation of other large scale screening programs, because many questions will be encountered in similar ways when screening and testing for other infectious diseases. In particular, we envisage the following articles as possible output:

• Epidemiological analysis of the data available in the Netherlands relating positivity and population prevalence
• Modelling study analyzing the temporal effects of population screening on the relationship between positivity and prevalence
• Modelling study analyzing the effects of acquired immunity on re-infection rates, positivity and prevalence

Manuscripts of these articles will be prepared by mid 2010. All publications will be prepared in close collaboration with the CSI project team and will include CSI project members as co-authors where appropriate.

Foreseen follow-up
On the national level, public health policy makers who have to take decisions on how to design future prevention strategies for Chlamydia infection will benefit from the results of this study.

On an international level, the results of this project will contribute to a better interpretation and evaluation of large scale chlamydia screening programs and will therefore benefit all countries that have already implemented or are planning to implement national chlamydia screening programs.

More generally, the analysis to be conducted in this project will contribute to evaluating large scale prevention programmes by generating insight into how well positivity of testing of a target population can represent population prevalence and what additional information is necessary to obtain reliable prevalence estimates.
Motivation
There are indications for increased prevalence of the bacterium *Rickettsia helvetica* in the Netherlands. These pathogens are maintained in natural cycles involving mammals and ticks. Ticks live on animal and human blood and are important vectors of diseases such as Lyme disease. *Rickettsia helvetica* was recently identified in European sheep ticks all over Europe. In our annual surveillance of tick-pathogens we have consistently identified *R. helvetica* in a high percentage of ticks over the last 5 years. The prevalence of *R. helvetica* was comparable to that of *Borrelia burgdorferi* (Lyme disease) and peaked up to 65% in certain areas. Human infections with *R. helvetica* have not been reported in The Netherlands, most likely because of unawareness and unspecific flu-like symptoms. These findings raise the question whether *R. helvetica* exposure through tick-bites constitutes a risk to human health. In this project research will be conducted to investigate if diseases caused by *R. helvetica*, are an emerging risk to public health.

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

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

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

Planned activities
The project can be divided in 4 main activities:

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

**2) Detection of antibodies to Rickettsiae in the Dutch patients**

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

**3. Molecular identification of different Rickettsiae species**

Several molecular targets for the sensitive and specific PCR amplification of different rickettsia species need to be established. Two essential and independent genes will be selected, and a PCR based technique will be set up. The different Rickettsiae genospecies in the Dutch tick population will be determined by Multi Locus Sequence Typing using Bionumerics. Finally, the prevalence of the different Rickettsia species in the Dutch tick population will be determined.

**4. Lateral gene transfer between Rickettsiae and ticks**

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

**Planned products**

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

**Foreseen follow-up**

This project will have benefits for the RIVM and the public health services in the knowledge of a field that have been reported as emerging in Europe. Aim of this project is to develop and implement assays to be better equipped to study these emerging bacteria. We try to implement the serological assays in ongoing SOR research regarding the development of proteomics based techniques because this system has enormous potential to be used as a tool to screen for many types of clinical syndromes or outbreaks.
Motivation
Food borne illness has been documented for several groups of pathogens that infect persons after oral ingestion. Viruses, and foremost noroviruses (NoV), are currently recognised as major food borne pathogens in industrialized countries. Contamination control often relies on methods detecting the presence of indicator organisms such as bacteriophages or E. coli. However, data obtained with these methods do not correlate with the presence of viruses. Moreover, molecular based tools to detect the presence of viral RNA (or DNA), does not necessary indicate infectious viruses. State of the art approaches are needed to obtain inactivation profiles for noroviruses (and other food borne viruses) to be able to determine viral infectivity reducing methods in the food production process and areas. Ultimately, this will allow us to draft protocols that will reduce the number of infections due to either food borne or environmental transmission.

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

Strategic and innovative aspects
The innovative aspect of this project is that human NoV strains will be used to determine the infectivity in stead of model viruses. The detection method is based on a novel low-shear-stress rotating cell culture system for three dimensional tissue-like aggregates.

An up to date tool-database system for the assessment of likelihood of food borne transmission of emerging viruses is relevant to enable implementation of effective intervention strategies. This approach is new and timely and the result will allow us to maintain our leading role in the world in the field of viruses and food safety.

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

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

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3 Related projects: V/230461/01/EV Transmission and control of enteric viruses, V/300100/07/AA Voedsel gerelateerde virusinfecties, ENVIRONET, V/330140/07/VO Virussen in Voedsel
• Develop criteria and features that determine the success of viruses for food borne transmission.
• Produce a tool to assess the likelihood of food borne transmission.

2. Production of protocols for intervention of the transmission of food borne viruses.
• Analyse food production chains
• Implement detection methods for viruses on food
• Assess viral load reduction in post-contamination treatments of foods.
• Test measures to prevent food contamination.
• Draft protocols to increase bacterial and viral food safety.

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

Foreseen follow-up
This project will contribute directly and indirectly to the production of science based protocols for the intervention of transmission of enteric viruses. As such the CIb (foremost LCI), the public health services (GGD) and food handlers and food industry will benefit from the results. Since part of the project will aim at developing, evaluating and implementing assays to study the effectiveness of intervention/inactivation methods for viruses, we will be better equipped in the future to produce data needed for risk assessment of emerging viruses. Additionally, the database that will be constructed for the assessment of likelihood of food borne transmission of viruses will be maintained and put to use if viruses do emerge.
Motivation
In the Netherlands, different animal species are infected with helminths such as *Trichinella*, *Toxocara*, *Echinococcus*, and *Ascaris* that can also infect humans. A study carried out at the RIVM showed that the *Toxocara* seroprevalence is 19% on average, with 4% to 15% in people younger than 30 years up to 30% in people older than 45. A recent serological survey revealed that pigs are often infected with *A. suum*. Dutch citizens could be exposed since eggs of *A. suum* have been found in sewage sludge that is widely used as fertilizer. Evidence from various studies suggests that helminths modulate the host immune response and affect other immunopathologies such as allergies. To get a better understanding of the mechanisms involved in the negative or positive correlation between allergic asthma and helminth infection, early immune responses have to be investigated in detail.

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

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

Strategic and innovative aspects
In The Netherlands serodiagnosis of infections with *Toxocara spp.*, *Ascaris spp.* and *Trichinella spp.* is only carried out at the RIVM. The use of purified antigens derived from different helminths will be crucial in the attempt to improve the currently available assays. Serodiagnostic assays with higher specificity and sensitivity may have worldwide application. Emerging evidence indicates that infection with helminth affect the outcome of allergic manifestations. Identifying parasite antigens capable of suppressing allergic manifestations will open possibilities to develop novel therapeutics to prevent allergic diseases.

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

**Evaluation of purified helminth antigens and synthesized neo-glycans on APC maturation and T cells stimulation.**
Different glycan molecules present in *T. canis* E/S antigen have already been identified in a previous study and have been synthesized. The effect of neo-glycans TSL-1 and gp45 on DC

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4Related project: SOR project Cib6: Diagnosis of human parasitic infections (Cib/LIS/PAM); Surveillance of parasitic animal infections (Cib/LZO/Parasitology).
and macrophage maturation will be followed by measuring expression of cell surface molecules and cytokine induction as mentioned above.

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

**Improvement of serodiagnosis of helminth infections**
Several antigens will become available during the first years of this project which will be used to improve the serodiagnosis of helminth infections.

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

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

Other foreseen products are:

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

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

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

The Cib/RIVM will also benefit from this project since the immunological studies carried out in this study fits within the efforts in stimulating and improving immunological research within the Cib/RIVM. This will materialize in the future in the form of publications in peer reviewed journals, additional grant applications, PhD thesis and in the field of diagnostics in SOPs describing new tools for the diagnosis of toxocariasis and trichinellosis both important for humans and veterinary parasitology.
Motivation
In recent years, Europe has seen several outbreaks of viral infection where contaminated food was implicated as vehicle of transmission. Although the associated diseases are so far mild, such outbreaks have economic implications to communities. The types of foodstuff most often implicated in viral disease outbreaks are those which are eaten raw or only lightly cooked, such as soft fruit, salad vegetables, and shellfish. Contamination of foodstuff can occur at different stages of food production. Current HACCP measures in food production are directed towards reduction of bacterial – not viral – contamination. The existence of enterically transmitted viruses from both human and animal sources, and susceptible routes whereby they may contaminate the foodstuffs, thus constitute a present threat to European food safety. Without active measures to monitor and control virus contamination of food, the impact of foodborne viral disease will remain, and possibly increase if current or new viruses emerge.

Aim of the project
The concept of VITAL is the integrated risk assessment and management of contamination of the European farm to market food supply chain by pathogenic viruses to:

1) acquire data on virus contamination of food and environmental sources suitable for quantitative viral risk assessment
2) assess foodborne viral risks for determining high risk situations and efficacy of interventions
3) develop new measures to prevent virus contamination of foods and the environment
4) develop and assess measures for virus reduction and control in case of virus contamination.

Strategic and innovative aspects
The output of the project relies on quantitative virological risk assessment, which in the end will direct the identification of good management practices that reduce viral contamination of foodstuffs. CIb plays a vital role in the output of the project by leading the data analysis work package, which includes the risk assessment. Because the quality of the risk assessment depends on the quality of included data, CIb will automatically play a vital role in the data gathering work packages by developing effective sampling schemes for the respective food chains. This provides CIb with a central role in the development of quantitative virological risk assessment, a currently unexplored discipline worldwide. Furthermore, within VITAL three PhD students are contracted, one of whom will be supervised by the RIVM. The assigned SOR budget will be used to fund this PhD-student and his/her research.

Planned activities

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5 This project is a cooperation between the RIVM and the Central Science Laboratory (UK), Veterinary Laboratory Agency (UK), Catholic University of Leuven (Belgium), University of Barcelona (Spain), Instituto Tecnológico Agrario de Castilla y León (Spain), University of Ljubljana (Slovenia), Veterinary Research Institute (Czech Republic), University of Helsinki (Finland), University of Patras (Greece), Instituto Superiori Sanita (Italy), Wageningen University and Research (Netherlands), National Veterinary Research Institute (Poland) and the Scientific Veterinary Institute “Novi Sad” (Serbia).
The project focuses on norovirus (NoV), hepatitis A virus (HAV) and hepatitis E virus (HEV) as specific foodborne viruses. As these viruses may be present at undetectable levels, source-specific adenoviruses (human, bovine and porcine) are monitored as well as indicators for faecal contamination from respective sources. The presence of these viruses will be examined during production, processing and retail for the following food chains in three or four different European countries: soft fruits, vegetables and pork. Furthermore, presence of viruses in shellfish will be monitored at retail in three different European countries. In addition to the monitoring of viruses along the food chain, effects of specific measures to reduce or eliminate viruses will be studied.

VITAL focuses on all phases of food production: primary production, processing and retail. Four distinct tasks will be completed within VITAL. First, a preparatory phase will be initiated to harmonize virus-detection procedures including proper internal and external quality controls, and to identify critical control points according to HACCP guidelines for the production and processing phase. Second, samples will be collected at these critical control points for each food production chain and analyzed for viral contamination. By assessing viral load before and after a critical control point, the increase or decrease of viral contamination can be estimated. In addition, laboratory and pilot-plant experiments will be conducted to obtain more refined virus-specific inactivation and reduction data for the control points. These studies are the three PhD projects initiated within VITAL. The SOR-funded PhD-student will specifically study virus inactivation. The data needs in the risk assessment will direct the choice of specific measures or treatments to study. Fourthly, data will be sent to CIb for statistical analysis and use in quantitative virological risk assessment. The final risk assessment model will subsequently be used to estimate effects of possible intervention measures. The effects will be evaluated ultimately in the field.

**Planned products**

1. Guidelines for collection of data that feed directly into quantitative viral risk assessments
2. A statistical tool to quantify virus counts and to estimate elimination and reduction of viruses due to treatment
3. Insight in virus inactivation and elimination for HAV, HEV, NoV and adenoviruses
4. A modular process risk model for quantitative virological risk assessment
5. Handbooks for the food industry prescribing HACCP measures that reduce virus concentrations

**Foreseen follow-up**

After handing the handbooks and protocols to the industry, actual effects of intervention measures on viral contamination of foodstuff should ideally be examined in the long run. Furthermore, prolonged support to the food industry is wanted to ensure correct and consistent implementation of proposed measures. A subsequent project may be initiated with interested partners.
Motivation
The National Survey of primary care is a continuation of the first and second National Survey of General Practice. These surveys are performed by the National Institute for Health Services research (NIVEL) in 1987 and 2001. Because the results are relevant for the RIVM, this institute cooperated in the Second National Survey. A special feature of the national surveys is that the demand for care and the supply of care are studied from the perspective of both patients and caregivers. The research therefore consists of several modules, as registrations of contacts between patient and doctor, interviews and videotaping of consultations.
The current project is a preparatory study for a third National Survey, by now called the ‘National Survey of primary care’. An important difference with the former two National Surveys is that the scope has been widened from the general practice to primary care in general. This means that the study also includes care by physiotherapists, primary care psychologists and obstetricians. The RIVM will also cooperate in this ‘third’ National Survey.

Aim of the project
The goal of this preparatory study is to write a project plan for the National Survey of primary care. This takes the following steps:

- Describe the societal developments and changes in the health care system
- Consult important partners in this survey: representatives of caregivers, patients and policy makers
- Incorporate research questions of scientific partners
- Formulating the research questions
- Work out the design and estimated budget of the survey

Strategic and innovative aspects
Investing in a new National Survey is of strategic importance for the RIVM, because this study delivers information for both the Public Health Status and Forecast and the Dutch Health Care Performance Report. These products come out at a continuous basis. Therefore it is vital that the information can be updated at a regular basis. One of the innovative aspects of this Survey is that it results in a continuous registration in primary care, just like the Second National Survey resulted in a continuous morbidity registration in General Practice. Other innovative aspects of this survey are the study of prevention in primary care and innovative forms of collaboration within primary care.

Planned activities
1. Describe the importance of the study in the context of societal changes, and make a first draft of the research questions.
2. Consult important partners in this field of study with the question what this study can mean to their practice. With this inventory we can refine the research questions.
3. Think through the design of the study and the budget.
4. Find financing for this project

Planned products
The product of this project is first of all a project plan describing the importance, the research questions and the design of the survey. The real product is of course a scheme for the performance of the National Survey in primary care, in such a way that the study can start in the beginning of 2009.

**Foreseen follow-up**
If this preparatory study succeeds, a new National Survey will be performed. This survey will bring relevant information for different products of the division of public health and health care of the RIVM. In addition, because the study is designed on the basis of questions from policy makers, care givers, patients and scientists, the results will be relevant for enhancing health and health care policy, practice and scientific research. Just like its predecessors, the National Survey will be the source of many policy documents, reports, scientific publications and doctoral theses.
Motivation

In vivo bioequivalence (BE) testing is the classical methodology for assuring efficacy and safety of generics. But in vivo BE testing is relatively expensive and reliable in vitro BE tests could be a very important contribution to the availability of affordable, yet effective and safe medicines. Amidon and co-workers (1995) developed a comparative in vitro dissolution testing of the generic drug product versus the innovator as a surrogate BE test. What, however, is lacking is a validated surrogate test able to detect differences in GI permeability in vivo between two drug products. BIOTHREE will develop such an in vitro BE test.

Aim of the project

BIOTHREE will develop a new in vitro BE test and hence extending the possibilities of in vitro BE testing to BCS Class III APIs.

Strategic and innovative aspects

Generic substitution is the single major tool available to limit the costs of pharmaceutical care. This holds for all countries, and also for The Netherlands as generic substitution is strongly promoted by the government and health assurance companies. So, biowaiving of BCS Class III immediate release drug products is important for all countries but most urgent for developing countries and a major objective of the WHO.

In addition to the scientific outcomes, the additional benefits for RIVM, will be:

• Ph.D. opportunity for an RIVM employee.
• Sponsored practical work for KCF laboratory.
• New field of competence for KCF laboratory: bioanalytics.
• More, and more important, assessments of claims of BE.

Planned activities

The methods used in BIOTHREE are the Caco-2 cell-culture membrane system will similar as the methods used at the Pharmaceutical Quality Research Institute (PQRI) in the USA.

• From the results of the two PQRI studies, three APIs from the five studied by the PQRI will be selected as model APIs for BIOTHREE.
• From the results of the PQRI studies 9 excipients studied in BIOTHREE will be selected.
• Reference drug products will manufactured from purchased innovator tablets that will be grinded and formulated in capsules.
• Worst-case test drug products will be manufactured; being the same grinded innovator tablets, but with added known amounts of excipients to be tested.
• From each model API, one reference product and two test products will be manufactured.
• Reference and test products will be manufactured under a license to produce clinical test material.

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6BIOTHREE is a project under the umbrella of the International Pharmaceutical Federation FIP, in cooperation with the WHO; International partners are: Universität Mainz and Frankfurt, University of Maryland, Mahidol University and TNO.
• Test and reference products will be subjected to comparative in vitro dissolution studies
• Test and reference products will be subjected to comparative in vitro Caco-2 transport studies.
• Test and reference products will be subjected to a comparative in vitro bioaccessibility profiling during GI passage in TNO’s gastroIntestinal Model (TIM).
• The results of the TIM studies will be integrated with the results of the Caco-2 studies using in silico modeling
• Test and reference products will be entered in three in vivo BE studies
• The results of the in vivo BE studies are compared to the results of the comparative Caco-2 testing.
• The results of the in vitro TIM studies alone and in combination with the Caco-2 studies will be compared with the results of the in vivo BE studies.

**Planned products**
The following scientific publications are foreseen:
• Permeability as a critical parameter in bioequivalence: a literature review.
• Comparative permeability testing by CaCo-2 as a surrogate for bioequivalence studies in humans.
• Comparative integrated approach of TIM and Caco-2 studies as surrogate for bioequivalence studies in humans.
• Comparative in vitro permeability testing as a predictor for bioequivalence.
• Ph.D.: Comparative in vitro permeability testing as predictor for bioequivalence
• Recommendations for revisions of the regulatory guidance’s.

**Foreseen follow-up**
See strategic and innovative aspects.
For this project, co-funding is needed, which is yet not assured. The project will start only if the sponsoring is allocated.
Summaries proposals SOR starting in 2009

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<tr>
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<tr>
<td>Project leader:</td>
<td>Arnoud Akkermans (VGC – BMT)</td>
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**Motivation**

Whooping cough (pertussis) is an acute respiratory infection, caused by *Bordetella pertussis*. It manifests as a protracted cough illness. Pertussis toxin (PTx) in its detoxified form (dPT) is an important component of both whole cell and acellular pertussis vaccines (ACVs). Different ACVs comprise different combinations of putative protective antigens of *B. pertussis*, but they all contain dPT as protective antigen. For safety reasons, it is imperative to ensure that the quantity of residual PTx in vaccines does not exceed permissible levels. Therefore, each batch of pertussis vaccine is subjected to extensive safety testing in animals: the histamine sensitization test. However, presence of residual PTx causes major distress, or even death, in the experimental animals. Development of an *in vitro* method is urgently needed. So far, several *in vitro* assays to detect PTx have been developed, but correlation of the functional *in vitro* test with the *in vivo* tests might remain poor. In the present research project, we propose to develop an alternative *in vitro* method, based on the published knowledge that PTx induces phenotypic changes in different cell types. We hypothesize that the phenotypic changes in cells induced by PTx are preceded by an altered gene expression profile: specific genes are either up- or down regulated. We aim to analyze these differential gene expression profiles using microarray technology. In turn, these marker genes may form the basis of a novel alternative *in vitro* test to quantitatively analyze PTx.

**Aim of the project**

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

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

**Strategic and innovative aspects**

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

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1. Related projects are: SOR project S/340010 ‘Toxicogenomics in risk assessment’ and EU-project EU project E/360040 ‘Europese Vrijgifte’.
The -omics based in vitro method might serve as a scientifically sound reference method for validation of possible future (cheaper) methods.

This project will strengthen RIVM’s position in future expert advice to regulatory entities.

The project helps BMT to get in contact with academia in the pharmaceutical field.

Planned activities
The research proposal defines three phases:

Phase 1 (Month 1 – 24): Identification of candidate marker genes in exposed cell lines
We will select a suitable cell line based on a thorough literature study. Besides sensitivity to PTx, suitability for validation versus the classical mouse model will also be taken into account. Selected cell line(s) will be exposed to pertussis toxin per se or final vaccine product spiked with a dose-range of pertussis toxin. Phenotypic changes in metabolism or cell growth will be used to design the test model. Secondly, cells will be exposed to the test “vaccines” in order to generate gene expression profiles using microarray technology. From these expression profiles, candidate marker genes will be identified by performing extensive data analyses.

Phase 2 (Month 25 – 36): Pre-validation of a subset of candidate genes.
Sensitivity and specificity of (a subset of) the candidate marker genes is determined using microarray technology. In this phase we will analyse how far the number of genes to be tested can be reduced without affecting the outcome of the assay. In this phase a choice is foreseen between qPCR and microarray technology.

Phase 3 (Month 37 – 48): In-house validation.
The new in vitro method will be subjected to in-house validation. This includes determination of specificity, sensitivity, precision, and robustness. Furthermore, correlation with the classical in vivo test method will be determined using available in vivo data, derived from ongoing batch release testing. BMT has ample experience in validation of methods (ISO17025 accredited).

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

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

Foreseen follow-up
If successful, additional inter-laboratory validation in cooperation with interested parties (e.g. ECVAM) is to be expected.

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

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

Specific objectives of the project
Objective 1a: Database describing (healthy) human subpopulations of interest in terms of physiological and biokinetic parameters (for instance age, BMI or ethnicity).
Objective 1b: Database describing specific groups or classes of chemicals based on relevant physico-chemical characteristics determining their biokinetics.
Objective 2: A generic PBPK-model to predict the internal dose in (healthy) human (sub)populations following exposure to different classes of chemicals and to compare the associated potential health impact in different subpopulations.

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

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

**Planned activities**

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

1. A literature search and international research programs will be screened to identify relevant databases and tools to model inter-individual anthropometric and relevant PBPK-models that have a more generic character.

2. Classes of chemicals will be defined predominantly based on various properties (e.g. physicochemical characteristics, slowly or rapidly metabolized) that are important for the fate of a chemical in the human body (absorption, distribution, elimination).

3. A ‘standard’ PBPK-model will be built containing both a rat and a human model. It will be examined which parameters are specific and crucial for these questions.

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

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

6. Organization of a workshop with stakeholders.

**Planned products**

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

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

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

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

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

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

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

**Foreseen follow-up**

The database will be valuable for future health assessments, either with or without modelling, and can be used for new assignments. The generic model will be used to answer policy driven questions in the future and will be supportive for health risk and health benefit assessments, especially for the ministries involved in these fields.
Title: **Timeliness of response during outbreaks**
Project number: **S/210076**
Project leader: **Mirjam Kretzschmar (CIb – EPI)**
Start: **01-09-2009**
End: **31-08-2013**
Total costs: **€322.500 (2009-2013)**

**Motivation**
In view of the threat of a future pandemic outbreak of any highly pathogenic pathogen strain, including influenza, with possibly devastating numbers of deaths, health authorities all over the world are designing plans to prepare adequate responses to such an outbreak. Possible intervention strategies for pandemic influenza range from treatment with antiviral drugs, contact tracing and isolation, increasing social distances by closing schools and other public meeting places, to vaccination. The use of mathematical and simulation models has become an accepted means to test and evaluate the effectiveness of different interventions. The effectiveness of a response in containing an outbreak is largely determined by three quantities, firstly the completeness, secondly the timeliness and speed of every link in the response chain, and thirdly the effectiveness and coverage of reaching individuals who are targeted by intervention. Completeness is determined largely by the awareness of reporting GP’s. Timeliness and choice of interventions are determined by the clinical course of infection and its transmission dynamics and by the diagnostic tools available to (rapidly) identify infected individuals. The problem of underreporting of infectious diseases may serve as an example for the interaction of infection, response chain and control measures. Another point of attention is the behavior of populations. Understanding and making use of the influence of social networks and the underlying mechanisms of decision in conflicts between individual and population interests will greatly enhance the ability of rapid response mechanism to adequately roll out public health interventions.

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

**Strategic and innovative aspects**
The first innovative aspect is the idea to dissect the transmission and response process into smaller interacting units and to look at the relationship between infectious agent and response in a generic way by viewing them as one interacting system. The idea to investigate the relationship between social network aspects of human behaviour and the implications for the effectiveness of outbreak response implies a combination of methods from social sciences and mathematics/statistics to come to new insights for public health policy. Investigating

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2 Related projects: the project is related to the ongoing SOR project Tracking emerging epidemics.
relationships on the regional level will give new insights into the relationship between the
demographic and ethnic characteristics of a population and the effectiveness of outbreak
response. Finally, we plan to use concepts from game theory and game theoretical aspects of
social network interactions, to develop a flexible way of thinking about response planning.

Planned activities
1. Classification based on literature review of known (emerging) infections according to
   their clinical and transmission features determining how an outbreak progresses and
   where response measures can intervene.
2. Identification of relevant response measures and description of the response chain.
3. Identification of crucial factors to quantify the reporting delay. Similarly,
   identification and measurement of factors determining patient delays.
4. Collection of empirical data concerning (a) clinical and transmission features
   identified in 1 for some selected (emerging) infectious diseases and (b) quantification
   of duration and effectiveness of steps in the response chain as identified in 2 and 3.
5. Collecting empirical data concerning regional differences in the response chain for
   (emerging) infectious diseases through the GGDs in the Netherlands
6. Description of steps in the response chain that are influenced by social networks of
   target population
7. Development of mathematical framework to describe interaction of outbreak and
   response chain
8. Calculation of size and extent of underreporting for a set of specific diseases, and
   modelling the effect of underreporting in timeliness of outbreak detection
9. Incorporation of social network effects into model
10. Investigation of game theoretical approach to effectiveness of intervention measures
11. Identification of weak links in the response chain, most effective intervention
    strategies depending on type of (emerging) infectious diseases, data needs for better
    evidence base of intervention
12. Formulating recommendations for improving effectiveness of the response chain and
    for formulating public health messages (social network and behavioural effects).

Planned products
The main product of the project will be a PhD Thesis consisting of at least 5 papers published
or publishable in international journals and two papers on size and effect of underreporting.
The papers for the PhD thesis could focus on: (a) a classification of infectious diseases in
terms of time scales of relevant dynamic processes and interventions; (b) model definition and
analysis of some example diseases; (c) case studies for specific infectious diseases based on
notification data (e.g. new influenza A\text{H1N1} notifications); (d) analysis of the possible
impact of contact tracing for specific infectious diseases (e) regional differences in the
effectiveness of response. Further products:
   • A mathematical model, to collect the relevant data for parametrizing the model and
to properly interpret the modelling results,
   • A tool for improving completeness and timelines of the reporting and response
chain.
   • Recommendations for regional improvements in the reporting and response chain.
   • Measurements of the effect of implementation of the improvements in the
reporting and response chain in different GGD regions.

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

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<td>Jacco Wallinga</td>
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**Motivation**

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

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

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

**Aim of the project**

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

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

Planned activities

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

Planned products

Publications in international peer-reviewed scientific journals:

2. Frequency of observed differences between pairs of infector and infectee: towards a joint likelihood function of the generation interval and the genetic distance.
3. Reconstructing missing links in completely reported infectious disease outbreaks: pneumonic plague as an example.
4. Reconstructing properties of asymptomatic, unreported and missing cases in incompletely reported disease surveillance: hepatitis B as an example.
5. Reconstructing transmission trees using likelihood-based methods and pair-based likelihood functions.
6. Inferring key epidemiological parameters, including effectiveness of interventions, from reconstructed transmission trees.

Foreseen follow-up

Direct applications of the tools developed in the proposed project could include the following:

- Making a scientifically sound statement of the probability that one case has infected another when such statements are required in court;
- Providing clear directions for which type of contacts to include and exclude in epidemiological contact tracing for control of tuberculosis;
- Assessing the impact of an intervention during an outbreak, using all collected epidemiological and molecular sequence data, even when a vast majority of cases is asymptomatic, even if few cases are sampled to obtain the molecular sequence of the cases.

3 Related projects: This project builds heavily on the expertise accumulated in the ongoing project, S/210046 “Epidemic Modeling of Molecular Data".
pathogen, and even if the various pathogen strains have evolved different epidemic characteristics.
Summaries proposals SOR starting in 2010

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

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

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

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

**Strategic and innovative aspects**
This project will strengthen strategic collaboration between RUVM, WUR, TNO en RIKILT.
By performing this project two new items are involved:
1. the application of similar biomarkers of exposure (e.g. serum concentration) and of effects (e.g. geneexpression) in both experimental animals and humans;
2. the use of transcriptomics to facilitate a direct extrapolation from effects observed in experimental animals to those that can be expected in humans.

**Planned activities**
The activities can be distinguished into several steps:
1. Bioavailability and internal dose. Using epidemiological data an inventory will be made of food items and supplements containing isoflavones.
2. Definition of relevant parameters for risk-benefit assessment. Mixtures of isoflavones will be tested in gene reporter assays using oestrogen receptor alpha (ERα) or -beta (ERβ) responsive cell lines, to study the estrogenic activity in comparison with the individual isoflavones (genistein, daidzein, glycitein). For this purpose different cell lines containing varying ratios of endogenous or transfected ERα and ERβ will be used.
3. Comparison of animal and human endpoints. In this step transcriptomic analyses will be used to link the toxicological and epidemiological data and to provide a direct comparison between effects in animals and humans.
4. Integrated ‘tox-epi’ risk-benefit assessment. The final phase of this project proposal
Planned products

For this project the following products are foreseen:

- paper(s) in peer reviewed scientific journals on *in vitro* effects of isoflavones in gene reporter assays (2011/2012)
- paper in peer reviewed scientific journal on *in vivo* gene reporter response (2012)
- paper in peer reviewed scientific journal on gene expression profiles (2013 or 2014)
- Ph.D thesis (2014)

Foreseen follow-up

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

Title: Adverse effects of circadian disruption

Project number: S/340001

Project leader: Dr. A. de Vries (VGC-GBO)

Start: 01-01-2010

End: 01-09-2010

Total costs: € 857,000

Motivation

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

Aim of the project

The general aim of this project is to investigate whether working in night shifts leads to chronic health effects via a disturbance of the physiological circadian rhythm. The relation between shift work schedules and breast cancer development in mice will be investigated.

Specific objectives:

- objective 1A: Assess the causal relation between disruption of the circadian rhythm versus the incidence and malignancy of breast cancer in a well-controlled animal model. 1B: Investigate in the same animal model which changes in hormonal- and gene expression levels occur as a result of day/night rhythm disruption.
- objective 2: Investigate in a well-controlled animal model whether the observed changes in hormone- and gene expression levels after day/night rhythm disruption as identified in objective 1B depend on the type of shift schedule applied, mimicking night shift regimens frequently applied in The Netherlands.
- objective 3: Investigate in a well-controlled animal model the underlying mechanisms of circadian disruption in more depth, to find novel biomarkers which ultimately improve the validity of the biological index as prognostic tool of circadian disruption in humans.

Strategic and innovative aspects

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

The proposed approach to analyze adverse effects related to working in night shifts is unique because...
• the use of an innovative, physiological relevant, mouse model mimicking spontaneous human breast cancer development;
• it addresses the effect of different shift schedules.

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

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

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

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**Title:** Health 10yrs post-disaster in Enschede  
**Project number:** S/609150  
**Project leader:** Dr. ir. L. Grievink (MEV-IMG)  
**Start:** 01-01-2010  
**End:** 31-12-2010  
**Total costs:** € 96.773

**Motivation**
Disaster research in the past decennia has provided a growing, yet very limited understanding of long term effects of disasters on the health of those affected. To the best of our knowledge, no long-term longitudinal studies (10 years or more) are available that assessed experiences, functioning and health of disaster victims. The result of this study will give new insight in longitudinally course of health problems and functioning after a disaster exposure. Insight in these long term health effects, as well as the course and their determinants, are highly relevant for governmental and local post-disaster health policies.
Two aspects are very important to know after an event like Enschede (2000): 1) the post-event interventions to be taken; 2) how long after the event special health care facilities for victims should be provided. These aspects are not mentioned in scientific literature. This fourth health survey study will be additionally to the 2-3 weeks, 18 months and almost 4 years post-disaster assessments. The outcomes of this survey and the pre-disaster information on health problems from the general practitioners enables to study the incidence of reported health problems.

**Aim of the project**
This project has two aims:
1. a fourth health survey, concerning examining health problems, functioning and care utilization, among affected residents of Dutch background (N~1100) of the Enschede fireworks disaster (May 13, 2000).
2. to increase the scientific knowledge base nationally and internationally of the long-term health effects, 10 years post-disaster.

The result of this project will be published in a peer-reviewed paper.

**Strategic and innovative aspects**
1. a health survey 10 years post-disaster (while having access to three earlier surveys and pre-disaster data), will significantly contribute to a key role and position of RIVM nationally as well as internationally;
2. the project will enable insight in the long-term effects on health, and its determinants, which is crucial for post-disaster health policies;
3. the Health Council of the Netherlands noticed two gaps of knowledge that will be solved by performing this project:
   • insight in the long-term effects on health, and its determinants, which is crucial for post-disaster health policies;
   • the prevalence of the medically unexplained physical symptoms and its determinants on the long-term;
4. this study provides evidence for the impact of long-term environmental effect on health;
5. this project follows the recommendations of the audit of Emergency Response Function (ERF) for Health Impact Assessments after Disasters, a few years ago.

**Planned activities**
There are four phases to be distinguished:
1. preparation/design of the study; the design will be very similar as to the second and third wave (first wave included biomonitoring and was organised at one location);
2. data collection;
3. data control and analyses; with respect to phase 2 and 3, we can rely on our experiences with the first 3 surveys, because the design of 10 years follow-up will be similar.
4. writing peer-reviewed paper

**Planned products**
A publication in an international peer-reviewed journal related to the results of the questions in this study:
1. what is the prevalence and incidence of (disaster-related) health problems at approximately 10 years post-disaster;
2. what is the course of health problems during the 4 surveys (from 2-3 weeks until 10 years post-event)?
3. what is the prevalence of the group who reported chronic (severe) health problems at all four waves?
Foreseen follow-up
Outcomes of this project can further be used for the regular RIVM project (health impact assessment after disaster) aimed at risk factors that enables early detection of those at risk to (chronic) health problems after a disaster.
There are still two research questions that can be investigated in a new project:
1. what is the prevalence of health care utilization at approximately 10-years post-disaster?
2. What are the risk factors of those with chronic health problems at approximately 10-years post-disaster?

Title: Set-up a monitoring acceptance NIP
Project number: S/210086
Project leader: Dr. H.E. de Melker (CIb-EPI)
Start: 01-10-2010
End: 31-05-2014
Total costs: €368.310

Motivation
The introduction of new vaccines is not automatically accepted by the public. Recent experience with the introduction of human papillomavirus (HPV) into the national immunization program (NIP) has shown that new vaccines can lead to a tense climate relating vaccine acceptance. Furthermore, besides known religious objections, a diffuse movement has emerged involving people who have critical views about vaccination, including highly educated parents and supporters of certain types of alternative medicine. Insight into determinants of parents’ and (child) health care professionals’ (HCPs, also including General Practitioners) attitude towards vaccination in an earlier stage – before the decision to introduce a new vaccine is made – is therefore important.

Vaccination coverage in the Netherlands has been closely monitored, however the overall compliance does not give information on the (changing) motivation to vaccinate or not. Parents who comply with the program might already have some doubts. Unexpected factors from outside the NIP can influence and alter the attitude towards vaccination quickly, e.g. epidemics, media, disagreeing professionals and anti-vaccination lobbying. It is therefore essential to monitor the determinants of acceptance of vaccination for both parents and HCPs. Recent experience has shown that HCPs are the most important source of information about vaccination for parents of young children. For HCPs it is challenging to keep up with all the changes in the NIP in order to properly inform the parents. With an appropriate monitoring system trends can be followed and innovative measures can be taken to timely intervene in case the acceptance of vaccination is decreasing.

Aim of the project
To design, set-up and evaluate an innovative system to monitor trends in the determinants of vaccination acceptance with focus on:
1. new candidate vaccines for the NIP (e.g. hepatitis B, rotavirus, chickenpox);
2. new vaccine schedules (e.g. for pertussis);
3. current vaccines separately by parents and HCPs.

Strategic and innovative aspects
By monitoring the determinants of acceptance of vaccination, new innovative communication tools can be developed and pilot tested in the near future to try to fulfil the information need. New is that CIb has to extend their expertise in the area of behavioural sciences which is needed to communicate with the professionals and the public. Strategic alliances with universities are necessary to warrant that this issue will be dealt with.

Planned activities
1. examine key determinants:
• Literature study
• Study on determinants for HPV vaccine uptake

2. Monitoring system 1 based on questionnaire data:
   • Developing two questionnaires, one for parents of infants less than one year and one for HCPs (including GPs)

3. Monitoring system 2 based on website research:
   • Setting-up the monitoring of websites and particularly blogs and fora. This monitoring system gives the opportunity to detect new ideas or misconceptions regarding vaccinations in a very early stage.

Planned products
1. Monitoring system based on questionnaires and website search
2. meer reviewed publications
3. PhD thesis

Foreseen follow-up
The knowledge generated by this project may be used by different key persons (child health care professionals, program manager NIP RIVM, Health Council, Ministry of Health Welfare and Sport, communication department of CIb).

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<tr>
<th>Title:</th>
<th>Effects of paracetamol on vaccination</th>
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<tr>
<td>Project number:</td>
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<tr>
<td>Project leader:</td>
<td>Dr. C.M. Janssen (VGC-GBO)</td>
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Motivation
In many European countries paracetamol is used prophylactically to reduce pain and fever associated with vaccination as a routine. Indications that paracetamol has immunotoxic effects have emerged. Recently published results suggest a negative influence on vaccination response in infants that were prophylactically administered paracetamol prior to vaccination to prevent fever while such effects in adults that received revaccination were less evident. In animal studies paracetamol suppressed several immune parameters. There are a number of potential mechanisms whereby the frequent use of paracetamol might influence the immune system.

It is unlikely, that producers of paracetamol will invest in evaluating potential adverse effects of paracetamol. However, if proven, such effects of paracetamol are highly relevant for health authorities who advise on the use of paracetamol as a prophylactic measure for vaccination-induced adverse responses, especially for children.

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

Strategic and innovative aspects
The innovative nature of this proposal lies in the new perspective on the use of paracetamol as an antipyretic.

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

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

**Planned products**
The following product are foreseen:
- the yield information will be shared with health bodies such as the Dutch Health Council;
- peer review publications;
- a PhD thesis;
- (inter)national symposium

**Foreseen follow-up**
The information yielded by this project will form a basis for advice regarding the application of paracetamol in conjunction with vaccination, which is in many other countries than the Netherlands the current routine for children, and is considered in the Netherlands. The information will be fuelled to health bodies such as the Dutch Health Council.

Based on the outcome of the project, an (inter)national symposium will be organised with a view on further dissemination of the outcome in the scientific and regulatory world.

**Title:** Carcinogenicity of growth factors

**Project number:** S/360003/09

**Project leader:** Dr. J.W. van der Laan

**Start:** 01-07-2010

**End:** 30-06-2014

**Total costs:** € 792,635,--

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

**Aim of the project**
The aim of this project is to define strategies for assessing the carcinogenic risk of recombinant human growth factors and their analogues. For this, we propose to use insulin
analogues as a model compound in relation to mammary gland carcinogenesis. The specific objectives of the project are:

1. to analyze *in vitro* the molecular and cellular responses induced by different insulin analogues.
2. to determine *in vivo* the carcinogenic properties of insulin analogues on mammary cancer development.
3. to define a set of ‘signatures’ of pro-mitogenic insulin analogues using gene expression profiling.

**Strategic and innovative aspects**

There are several strategic and innovative aspects to mention:

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

**Planned activities**

- specific objective 1: To analyze *in vitro* the molecular and cellular responses induced by different insulin analogues. We anticipate that insulin analogues may act through the insulin-receptor and/or the insulin-like growth factor receptor (IGF1R). Here we will systematically evaluate the role of IR and IGF1R in insulin analogue signaling in a panel of human mammary epithelial cells that selectively express either the IR or the IGF1R receptor.
- specific objective 2: To determine in vivo the carcinogenic properties of insulin analogues on mammary tumor development. Ultimately we anticipate that *in vitro* models should be able to establish the differential activation of insulin analogues of the IR and IGF1R.
- specific objective 3: To identify specific signatures of pro-mitogenic insulin analogues using gene expression profiling. These proposed experiments will ultimately reveal the specific preference of a selected set of insulin analogues for either the IR or IGF1R. We will use IR and IGF1R human breast cancer cell lines developed under objective 1 to define gene expression (signature) profiles that can discriminate between either IR or IGF1R activation. Furthermore, we will use tumor material from objective 1 to determine the correlation between the predictive pathways activated by IR and IGF1R under *in vitro* conditions with the *in vivo* situation.

**Planned products**

Two products are planned:

- Ph.D.Thesis
- publications in peer-reviewed scientific journals

**Foreseen follow-up**

Review of the feasibility of the application of these approaches in regulatory drug safety evaluation on a European and global scale (EMA/CHMP and ICH). The CHMP points-to-consider-document on the non-clinical assessment of the carcinogenic potential of insulin analogues (2001) is requested to be updated.

Better risk estimation of long term hormone use in diabetes 2 patients in relation to the occurrence of mammary tumors.
Motivation
The therapeutic effect of medicines is not only determined by the pharmacological properties of the active substance. The perception of the patient may also play a crucial role. Even without inclusion of any pharmacologically active substance in a pharmaceutical dosage form, a therapeutic effect sometimes is observed: the ‘placebo effect’. But patients can also have a negative perception, resulting in worsening of the disease and/or symptoms, or side effects. For example, switching from innovator to generic carbamazepine tablets caused an increase in side effects in patients. One of the postulated explanations was the negative perception of the patients towards the cheaper generics. This negative perception effect is called the ‘nocebo effect’.

Aim of the project
The aim of this explorative literature study project is to review the measuring techniques that are currently available for the measurement of nocebo effects. Knowledge on these techniques is necessary in order to investigate and estimate the consequences of nocebo effects for public health.

This project is to be considered as pilot project to subsequent research into the estimated consequences of nocebo effects for public health.

Strategic and innovative aspects
- the project is innovative because studies on nocebo effects of medicines are rather limited (In Pubmed only 95 publications were found with the search term ‘nocebo’).
- the importance of consumer behavior with respect to health care systems is growing and RIVM should keep track with these developments.
- Exploring and gathering knowledge on nocebo effects will give the RIVM a better position for international collaborations.
- the knowledge gained in this project will serve the policy making process and policy evaluation of the Ministry of Public Health in the policy area of medicines.

Planned activities
The activities can be divided in the following major steps:
- literature search
- publication of a scientific paper including consultation of experts and reviewing by colleagues (internally as well as externally)

Planned products
- a literature review on the current knowledge available on nocebo effects, including an overview of all available methods (measurements techniques) to determine the nocebo effects (including pros and cons of each method).
- the obtained knowledge will be used to acquire a research project on the public health implications of nocebo effects in substitution of medicines.

Foreseen follow-up
The knowledge gained in this project, and subsequent related projects, will serve the policy making process and policy evaluation of the Ministry of Public Health in the policy area of medicines.
Knowledge of the impact of nocebo effects on public health will be internationally relevant. Acquired knowledge will give the RIVM opportunities to share and extend this knowledge in international settings.