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

Results and significance of the RIVM Strategic Research 2007-2010

Prepared for the future

RIVM Report 000201102/2011

W.J.G. Lijs-Spek | J.M.H. Demon | J.Mos

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Colophon

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This investigation has been performed by order and for the account of Director - General RIVM, within the framework of the RIVM Strategic Research

Abstract

Results and significance of the RIVM Strategic Research 2007-2010
Prepared for the future

In this document, the National Institute for Public Health and the Environment (RIVM) reports on four years of RIVM Strategic Research (SOR).The strategic research programme helps the institute to anticipate upcoming questions of its primary principals, to ensure the quality of its scientific expertise and to participate fully in international research networks. The outcome of all projects from the period 2007-2010 is presented.

86 projects have been executed, grouped into 6 strategic themes. Approximately 30% of the projects continue after 2011; the preliminary results of these ongoing projects are described.

This strategic programme has provided a variety of new instrumentation, data, knowledge and improvement of existing instrumentation and knowlegde of public health and envrionment. The results contribute to the core business of RIVM. Apart from this, new scientific networks have been established and existing networks have been strengthened. Over 350 scientific publications have been published in peer reviewed magazines.

Keywords:
strategic research, innovation, scientific impact, societal impact, future, knowledge, instrumentation

Rapport in het kort

Resultaten en betekenis van het Strategisch Onderzoek RIVM 2007-2010
Voorbereid op de toekomst

Dit rapport brengt verslag uit van vier jaar Strategisch Onderzoek RIVM (SOR), het eigen onderzoeksbudget van het RIVM. Het SOR-budget is bedoeld voor onderzoek om het RIVM te voorzien van de benodigde expertise en kwaliteit, zodat het nu en in de toekomst taken voor opdrachtgevers adequaat kan uitvoeren. Het rapport geeft de inhoudelijke resultaten en toepassingsmogelijkheden weer van alle projecten over de periode 2007-2010.

In totaal zijn in de onderzoeksperiode 86 projecten uitgevoerd, onderverdeeld in 6 strategische thema's. Ongeveer een derde deel van de projecten loopt nog door na 2011; de voorlopige resultaten van de lopende projecten zijn hier vermeld.

De resultaten van dit SOR-programma bestaan uit een schat aan nieuw instrumentarium, nieuwe data en kennis, en verbetering van bestaand instrumentarium en bestaande kennis op het gebied van volksgezondheid en milieu. Deze resultaten dragen in belangrijke mate bij aan de uitvoering van de huidige kerntaken van het RIVM. Daarnaast zijn veel wetenschappelijke netwerken verstevigd en nieuwe verbindingen aangegaan. Het programma heeft ruim 350 publicaties in peer reviewed wetenschappelijke tijdschriften voortgebracht.

Trefwoorden:
strategisch onderzoek, innovatie, wetenschappelijke impact, maatschappelijke impact, toekomst, instrumentarium, kennis

Contents

Summary

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

The Strategic Research Programme is set up using four-year programme cycles. The programme 2007-2010 comprises 6 strategic research themes, which together cover 86 individual research projects. Most of the projects of cycle 2007-2010 have been completed by December 2010. Therefore most of the results and products are available by now.

The results of the programme 2007-2010 have significantly contributed to RIVM's skills needed for its core tasks. RIVM is a large institute with a wide variety of tasks and works on main public health issues, like infectious diseases, chronic diseases, healthy ageing and environmental threats.

A core task of RIVM related to these main issues is to assess a variety of risks, e.g. pathogens, chemical exposure, drugs, radiation and diet. Adequate risk assessment methods are urgently needed. The strategic research has contributed largely to the development of new methods and the improvement of existing methods. Numerous models are available now, which are helpful to get a quick assessment of complicated situations. New techniques, like genomics, proteomics and sequencing have been made suitable to answer the questions of the principals. Also special attention was given to the development of instrumentation for rapid assessment, as required in cases of emergency. New guidelines were developed by using the outcome of Strategic research projects.

RIVM's strategic research aims to be applicable within five to ten years, but some projects appeared to be just in time. The models that resulted from these projects have been used in relation to, e.g., the Q fever epidemic, the new flu and the assessment of air pollution from a Dutch steel plant. New guidelines have been developed by using of the outcome of Strategic research projects.

Through the strategic research, RIVM has been able to set up new collaborations, or strengthen existing collaborations with national and international partners. The programme resulted in 353 peer reviewed publications (December 2010). Part of the strategic budget has been used to cofinance European projects. In this way, RIVM strengthened its scientific position and network.

In general, the results of the presented strategic research projects have served their goal to prepare RIVM to future tasks.

1 Introduction

1.1 The RIVM Strategic Research

A dedicated budget for strategic research enables the National Institute for Public Health and the Environment (RIVM) to anticipate upcoming questions of its primary principals, to ensure the quality of its scientific expertise, and to participate fully in international research networks.

The largest share of RIVM's activities focuses on today's questions. Important clients, such as the Dutch Ministry of Health, Welfare and Sport and the Ministry of Infrastructure and the Environment, ground their policies in knowledge collected by the institute. In the future, these very same clients will continue to need prompt answers to urgent policy questions. To prepare itself for such future requests, according to best scientific practice, RIVM has an earmarked budget for research into long–term research questions. Its Strategic Research Programme (SOR) enables the institute to serve its clients quickly and adequately tomorrow just as it is doing today.

The Strategic Research Programme is set up using four-year programme cycles. The programme 2007-2010 comprises 6 strategic research themes, which together cover 86 individual research projects. Most of the projects of cycle 2007-2011 have been completed by December 2010. Therefore most of the results and products are available by now.

1.2 Significance of strategic research for RIVM

RIVM is the Netherlands' largest public knowledge institute in the areas of public health, environment, safety and nutrition. Its primary task is to support the Dutch government in making science-based policy by providing sound and independent counsel. RIVM's advice typically reflects a large body of scientific evidence and often builds on full risk assessments or risk management procedures.
In addition, RIVM carries various executive responsibilities in the areas of national health and the environment. RIVM's other (international) clients include public organisations such as the World Health Organisation (WHO), the European Commission (EC) and various agencies of the European Union (EU).

Thanks to its strategic research, the institute is able to anticipate situations that may arise in the future, such as outbreaks of chronic diseases or changing health risks, due to ageing populations or global warming. The annual budget for such research averages about 13 million euros. By laying strong scientific foundations, RIVM will be able to answer questions high on the agendas of policymakers five to ten years from now.

Long–term funding is also crucial to safeguard the institute's lasting scientific quality. Building international scientific partnerships, participation in international collaborations and publishing research articles in high-ranking peer reviewed journals all require more time and financial certainty than short–term, demand–driven projects can provide on their own. The institute as a whole needs a strong reputation in order to attract high–quality scientists, who in turn are essential for gaining scientific authority.

Public health and the quality of the environment are central to RIVM's public tasks. Companies or universities may choose to bypass some lines of research, even when society could benefit from their results. Having a strategic research programme enables RIVM to pursue questions even if success cannot be guaranteed in advance.

1.3 Strategic themes

RIVM's strategic research must fit within a limited number of carefully chosen research themes. They serve as the Strategic Research Programme's overall framework. Research themes must align with RIVM's strategic areas and should anticipate future developments. The six themes of the 2007-2010 Strategic Research Programme were chosen in 2006. Much of RIVM's research is multidisciplinary, so overlaps between themes and programmes do occur. The themes were chosen in close consultation with the RIVM's Scientific Advisory Board.

Most themes have grouped various projects into distinct research programmes. Appendix 1 provides a full list of programmes and projects.

1.4 Reading guide

In the next six chapters the six strategic themes are described. In each chapter, consecutively, three subjects per theme are discussed: the original objectives, the overall outcome, and finally, the results of the individual projects are summarised.

Appendix 1 provides a list of all projects.
Appendix 2 provides an internet link to the full list of publications.

2 Theme: Risk assessment, perception, consumer behaviour and understanding (RPC)

2.1 RPC objectives

Studies into risk assessment, risk perception and consumer behaviour are highly relevant to many issues in society today. Research within this theme affects one of RIVM's core competences and is therefore important to most if not all of the institute's divisions. The theme offers many opportunities for interdivisional cooperation.

Programmes
Research projects in this theme are grouped into two research programmes:

- Experimental studies focussing on properly estimating risks and reduction of our dependence on laboratory animals.
- Information to consumers.

2.2 Summarised outcome of RPC

The 'Risk assessment, consumer behaviour, perception and understanding' projects have led to an increased knowledge on the fields of estimating risks, reduction of the use of laboratory animals, and information to consumers. The RPC theme comprises ten projects covering a wide range of research areas including modern tools for risk assessment, like toxicogenomics and proteomics, PBPK modelling, effects of nanoparticles, development of alternative (less animal demanding) toxicity tests, consumer behaviour and development of performance indicators for quality improvement of intensive care facilities. Six projects are still continuing in 2011 or beyond. The results of seven projects are mentioned. Three projects, that started only recently in 2009 and 2011, are not described. All project titles are mentioned in Appendix 1.

Experimental (animal) studies in risk assessment
Risk assessment is a major business of RIVM. Adequate and more innovative tools are urgently needed. Progress has been made on the development of new risk assessment techniques, like proteomics. Proteomics is a relatively new and promising technique, and was shown to be useful for cancer screening and prenatal Down's syndrome screening. An important step forward has been made into putting the proteomic technique into practice. This is also the case with the toxicogenomics technique: a proof-of-the-principle has been given. Healthy food is essential for a healthy life, without chronic diseases. To improve dietary risk assessment, new methods, that allow better estimation of dietary exposure than previous ones have been developed. This is important because the current diet in the Netherlands differs considerably from the desired healthy diet, and it is to be expected to become even worse in the near future.

For several reasons animal testing in risk assessment is needed to be replaced with alternative tests. Three different models have been developed, which may contribute to the reduction of use of laboratory animals. Furthermore, thorough studies have been performed to establish presumptive toxic effects of nanoparticle exposures. Nanoparticles are being increasingly used in a wide range of consumer products. Cytotoxic effects were indeed found, especially with silver nanoparticles.

Information to consumers
The socio-technological and epidemiological trends urged for deeper and broader thinking about the implications of web-based and mobile technologies for (public) health and health care. Knowledge on online information behaviour has been gained and e-tools and e-services for patients have been developed.

To support health care professionals and institutions to perform better, performance quality indicators and performance schemes must be developed and implemented. Fifteen barriers to using performance data for systematic quality improvement were identified. This identification is the starting point for the development of a quality improvement programme.

2.3 RPC project results

In Appendix 2 an internetlink to the full list of publications is provided. The list will be updated on a regular basis. The project numbers are mentioned below and in the list of publications.

S230136 Ing. J.H.J. Reimerink Proteomics for population screening
In the Netherlands the RIVM plays an important role in coordinating and in some cases executing and/or validating several large-scale population screening programs and ad hoc screenings in case of infectious outbreaks. In the future there is a need for new sensitive screening methods with less false positive and negative results. RIVM explores the potential of new innovative proteomics techniques for screening purposes, and develops new innovative assays within this project for early detection of disease biomarkers in human body fluids.

These assays are especially oriented towards breast cancer- and prenatal Down's syndrome screening. For the detection of immunological responses to pathogens, the RIVM develops serological assays that allow simultaneous screening on the presence of antibodies to groups of viruses that have been implicated or suspected as causes for different clinical syndromes.

The developed and implemented proteomics techniques allow less invasive sample collection like finger prick blood or saliva by the possibility of simultaneous screening of many biomarkers or human antibodies to different viruses: multiple marker testing. Methodologies for antibody and antigen array spotting and protocols for serum labelling and detection were set up and will be available to a broader RIVM research group through the Proteomics Platform. In conclusion these new techniques allow fast and non-invasive testing of multiple diseases simultaneously. Improving the performance of large-scale population screening programs has evident significance for public health.

S340010 Dr. M. Luijten Toxicogenomics in risk assessment
It is obvious that time has come to act more innovative to toxicity testing. The new approach needs to be quicker, cheaper, and less demanding with respect to animal welfare. Toxicogenomics is the study of responses of the genome (the whole of genes) to hazardous substances, by using new technologies. With genomics data the identification of the mode of action (MOA) and the potential toxicity of chemicals can be determined better and faster than before.

An *in vivo* study with a PVC softener (phthalates) showed that, by using toxicogenomics, differences in gene expression indicative for the type of exposure, can be detected earlier or at lower doses than by observing tissue damage. These findings are promising for 'early warning' biomarker analyses

and for using toxicogenomics in a category approach. Also transcriptomics analysis (a technology to detect genome-wide mRNA expressions) showed significantly altered gene expression profiles immediately after exposure and shortly thereafter. However, after a prolonged recovery period, the profiles were comparable to controls.

Toxicogenomics is one of the new promising technologies that could transform the current approach of risk assessment, as demonstrated by the results of this project. The potential use of toxicogenomic information at different stages of the risk assessment process is clear: a proof-of-principle for the possibility to implement toxicogenomics in hazard assessment is given. Furthermore, the first step towards interpretation of changes in gene expression has been made.

S350010 Dr.ir. M.C. Ocké Methods for dietary exposure assessment
Healthy food is essential for a sound weight and body, cardiovascular diseases, diabetes and various types of cancers. For example, dietary recommendations propose to consume less than 10% of saturated fat and more than 200 grams of vegetables daily. The current eating habits in the Netherlands, considerably differing from the desired diet, lead to a great health loss and an annual loss of approximately 300,000 - 400,000 disability adjusted life years (DALYs). These trends are supposed to increase in the next 15 years. Dietary risk assessment is essential for policymakers and important for public health.

To improve dietary risk assessment a mathematical model was developed. This statistical methodology better translates the data collected in food consumption surveys. With this software the population distribution of *usual* intakes (biologically relevant intake) can be estimated using repeated measurements of *short-term* intake (intake as measured in food consumption surveys). A new feature is the possibility to combine intake from foods and intake from dietary supplements. In addition, statistical methodologies to combine different sources of information and to quantify uncertainties were developed. Using these methodologies, the effects of salt reduction scenarios were estimated.

These improved and extended statistical methods allow a better estimation of dietary exposure than previous methods Good methodologies for assessment of dietary intake or exposure are essential for an adequate policy aimed at a healthy nutrition and safe foods.

S34050 Dr. L.T.M. van de Ven Alternatives for animal testing
In hazard identification and risk assessment of chemicals and drugs, *in vivo* animal testing plays a crucial role. In view of ethical reasons, public and politics request the replacement of this toxicity testing with alternative tests. Other stakeholders support this ambition because of scientific and financial reasons. The application of new tools, such as improved cell culture techniques and genetic analytical techniques, gives the opportunity to even improve the quality of these assessments.

This project contributed to the development and validation of several alternative testing models. Three of such models identify different toxic properties of chemicals for the liver. One model employs the *in vitro* culture of liver cells from transgenic animals which are particularly sensitive for potential carcinogenic properties of chemicals. Another *in vitro* system consists of embryonic stem cells which are induced to develop into liver cells and can then be used for toxicity testing. A third model employs three-day old zebra fish embryos for the same purpose. All three models use molecular markers (‘toxicogenomics’) to improve

their potential to identify liver toxicity and to validate them as new *in vitro* systems as replacement for *in vivo* models. Toxicogenomics proved to be a major asset to alternative testing models, enabling sophisticated and discriminative evaluation of toxicity.

Thus, these three different models, which complement each other, may contribute to reduce the use of laboratory animals in toxicity testing, and simultaneously improve assessment of risk of exposure to chemicals for humans.

S340030 Dr. W.H. de Jong Nanotechnology, potential risks
Nanotechnology makes it possible to work with materials as small as nanometers (one billionth of a meter). The small size is accompanied by special characteristics such as increased chemical and physical activity that makes nanomaterials attractive for many applications including consumer products, medical technology, food technology, environment and agriculture. Nanotechnology involves advantages, but there is uncertainty whether the increase in reactivity may also result in an increase in negative, toxic effects for man and environment. An integrated approach is needed for hazard identification and risk evaluation, and the ultimate risk assessment of the use of nanomaterials.

The RIVM has studied the possible toxic effects and the environmental behaviour of various nanomaterials. The focus of the research was whether a decrease in size indeed results in an increase in toxicity. In the project nanosilica, nanosilver, and nanogold were investigated for their toxicity in various test systems. The most toxic nanomaterial was nanosilver that is used for its antibacterial activity, whereas nanosilica was only toxic at (very) high concentrations, and nanogold was not toxic at all. The behaviour of cerium nanoparticles in an aquatic environment was studied. In water the distribution of cerium oxide was found to be dependent on the amount of organic matter in the water. Organic matter in the water was able to stabilise the presence of nanomaterials in the water.

In conclusion, some nanomaterials like nanosilver indeed induce toxicity whereas other nanomaterials were not toxic at all (nanogold) or only toxic in very high (unrealistic) concentrations. For nanosilver in some assays a size effect was observed showing that the smallest particles were more toxic than larger particles.

S270126 Dr. H.C. Ossenbaard gettingBetter.nl
This is RIVM's first strategic research project in the field of consumer health informatics and eHealth. It arose in the wake of kiesBeter.nl (2005), a major assignment in health information and communication comprising a national health and care portal for a general audience. The socio-technological and epidemiological trends urged for deeper and broader thinking about the implications of web-based and mobile technologies for (public) health and health care.

In close cooperation with the Centre for eHealth Research and Disease Management (University of Twente) gettingBetter.nl explored two research questions at the crossroads of health, technology and social science. The first concerns online information behaviour including (e-)health literacy, motivation, online decision making, and usability. Outcomes were used to improve RIVM's informational products such as kiesBeter.nl. The second regards development,

design, implementation and evaluation of e-tools and e-services for patients or professionals, e.g. virtual coaches and business modelling. Results were used to build a wiki for online collaboration in order to improve the measurable impact of eHealth technologies.
The project contributes to the strategic positioning of RIVM in the changing landscape of (public) health and information and communication technologies by creating and sharing knowledge at an international level

S260196 Prof. dr. G.P. Westert Effective use of performance indicators
To support health care professionals and institutions to perform better, performance quality indicators and performance schemes must be developed and implemented.

The RIVM has developed the project Information feedback on quality indicators (InFoQI), a quality improvement programme with feedback reports as the basic element to promote the use of the Plan-Do-Study-Act cycle (PDSA) at Intensive Care Units (ICUs) to guide organisational changes. Fifteen barriers to using performance data for systematic quality improvement were identified by literature studies, a validated questionnaire and an expert meeting. These barriers formed the starting point for the development of the quality improvement programme. The setting of the research was the Dutch ICUs and the National Intensive Care Evaluation (NICE) registration.
Twelve of the identified barriers were targeted by InFoQI. The ICUs participating in this program establish a local multidisciplinary quality improvement team. The team's main tasks are to formulate a quality improvement action plan based on their baseline performance data and to monitor their performance using monthly and quarterly feedback reports.

InFoQI is developed to overcome barriers to using performance feedback for improving the quality of intensive care. Its effectiveness will be further evaluated in thirty hospitals/ ICUs.

3 Theme: Emergency response functions and safety (ERF)

3.1 ERF objectives

In today's world, governments need to prepare for emergencies. Whether they involve chemical, biological or radiation exposures or other types of calamities, all such emergencies require sensible preparation for an adequate response. In recent years, bioterrorism and infectious disease outbreaks have attracted attention. Other needs include modelling of environmental risks from chemicals or radiation, and research into toxicological effects in humans as well. RIVM needs to be fully up to date on safety and emergency response functions.

Programmes
Research projects in this theme are grouped into three programmes:

- Measurement and modelling;
- Risk assessment methods in emergencies;
- Clinical toxicology.

3.2 Summarised outcome of ERF

The ERF theme comprises eight projects, focussed on risk assessment in all phases of the safety chain. Three projects are continuing in 2011 or beyond. All results are mentioned, including preliminary results of the ongoing projects. All project titles are mentioned in Appendix 1.

Measuring and modelling
Rapid response in emergency is crucial, whatever is happening: bioterrorism attacks, chemical attacks or nuclear accidents. All require adequate assessment methods. Often the agent or the extent of exposure to the substance is unknown. To help in acute situations new screening approaches were developed, combining different analytical techniques. A new micro array technique was developed to screen effectively for bio threat bacterial pathogens, which already has been used in the assessment of the Q fever epidemics in de Netherlands. Furthermore a coherent package of rapid assessment methods in case of disasters, including a checklist and a decision making procedure, was made.

At the other end of the safety chain, realistic models for estimating risks are important in the prevention, without obstructing unnecessary spatial developments, as is sometimes the case with current guidelines. New criteria for the evaluation of technical measures in a quantitative risk assessment have been developed.

Risk assessment in emergencies
During large-scale emergencies quantitative risk assessments are a decisive factor in the determination of an effective countermeasure strategy. An adequate response in radiological accidents is now possible, because of the development of techniques on spatial mapping of radioactivity that were incorporated in the existing dispersion model.
Two methods for testing and sampling of volatile organic substances were developed and were already used during large incidents that happened in the Netherlands in recent years.

Clinical toxicology
Progress has been made on human toxicology. For instance, interesting results are obtained about the cellular effects of amphetamine and cocaine, which were contradictory to what previously had been assumed. The results of this project help to get more insight in the individual susceptibility in case of exposure to xenobiotics and the mechanism involved. This knowledge is being used to improve the information supply of the National Poisons Information Centre.

3.3 ERF project results

In Appendix 2 an internetlink to the full list of publications is provided. The list will be updated on a regular basis. The project numbers are mentioned below and in the list of publications.

S330006 Dr. B.J. van Rotterdam Biothreat DNA microarrays
An attack of bioterrorism or a biocriminal event requires a rapid response. Therefore accurate and simultaneous detection of a wide range of possibly used biothreat (pathogenic) micro-organisms in complex samples is highly desirable. The diagnostic system must be able to detect both known and unexpected pathogens.

Successful identification requires a prior knowledge of the identity of the contaminating organism. DNA microarrays, which enable the simultaneous interrogation of thousands of genetic elements, make these parallel and high-throughput screening capabilities possible. Besides specificity, sensitivity of the developed methods is also crucial.

RIVM developed two different array based methods for screening of four biothreat bacterial pathogens within 4-5 hours, without yielding false positive or false negative results. Of the two developed systems one system performs very well with regard to sensitivity, specificity, analysis time, sample handling, sample consumption and userfriendlyness, and can be used to increase the number of biothreat pathogens that can be screened for in the case of a bioterrorist attack.

Using the acquired knowledge and technology it will be relatively easy to develop similar robust microarrays for the detection and rapid subtyping of other pathogens, e.g. regarding the current ongoing Q fever epidemic in the Netherlands.

S620001 Dr. P.A.M. Uijt de Haag Quantitative risk assessment
Quantitative risk assessment for land-use planning in the Netherlands is more used as a standardised procedure than as a realistic risk evaluation. This view point is inspired by the fact that it is difficult to incorporate risk reducing measures in the QRA. To make the risk assessment more meaningful, an approach must be developed to value risk reducing measures correctly in the QRA.

To realise correct use of the QRA RIVM has started a benchmark, investigated technical measures and developed a protocol for the evaluation of technical measures. The risk of a fictitious storage depot of flammable liquids was calculated in a benchmark according to the French and Dutch regulations. The French regulations require a specific evaluation of technical measures in the risk assessment. Although the French method is significantly different, the risk

outcomes and their consequences for permitting and land-use planning are quite similar. This supports the choice of the prescription of QRA in the Netherlands. Secondly, methods to value technical measures in a QRA were evaluated using an atmospheric storage tank as example. The study concerned the effects of preventive technical measures on the failure frequency and mitigating technical measures affecting the consequences of the release of a dangerous substance. An approach is feasible, where information on the failure mechanisms attributing to each standard scenario and their relative importance is used, in combination with the effect of the technical measure on the different failure mechanisms. However, the outcome strongly depends on the basic assumptions.

The study resulted in a step-by-step guideline with the criteria for the evaluation of technical measures in a QRA, like overfill protection, highlighting the limiting conditions.

S630007 Drs. F.S.M. Stom Rapid assessment after disasters
A role of the government after disasters is to protect and restore public health. Following a disaster, public health decision makers need adequate information on possible (negative) health effects due to exposure or other disaster related events. Similarly healthcare workers request rapid insight into health status and healthcare needs. In the decision making process, rapid assessment methods are needed to collect information that is immediately required for decision making.

RIVM developed a coherent package of rapid assessment methods for application in disasters (radiation, nuclear and chemical agents and experienced shocking events): an updated checklist and a procedure for decision making on the application of biological monitoring. A new guideline on biological monitoring after small-scale chemical incidents will be finished. Furthermore two questionnaires were developed. The first is a questionnaire that combines registration of persons concerned with questions on health impact. The other questionnaire is developed for measuring non-specific symptoms and the attribution of these symptoms.

The project has strengthened the position of the RIVM as one of the leading institutes on post-disaster response for public health and psychosocial care. This is exemplified by the fact that the current strategy on rapid post-disaster response in the Netherlands will be presented at the World Congress on Disaster and Emergency Medicine.

S609001 Dr. S.M. Hoffer Terrorist attacks
In case of a terrorist attack with chemical agents a toxic screen in blood must make a rapid identification of the toxic substances, whether the agent is unknown or the extent of the exposure to a known toxic is uncertain. Exposure information like this helps health officials to demonstrate that exposure has occurred and to identify cases of non-exposure. This improves health effects investigations by delivering input to the human health risk assessment.

In this study a screening strategy has been developed using a select agent list. Within this project a selection of toxic industrial chemicals which are available in large quantities in the Netherlands was created. Aiming the screening strategy at such a list will not only improve the preparedness to terrorist attacks but can also be applied in case of exposure during industrial accidents.
The strength of the developed screening approach is the use of three different analytical techniques. When integrated together they cover the full range of

agents of the list without loss of sensitivity and performance. The whole strategy is focussed on achieving fast results. After a sample is taken it is split in four portions and all the different analysis techniques will run in parallel.

Although the use of this screening may result in improved exposure assessment, further study is essential. RIVM together with the Regional Public Health Centres and first responders are currently exploring if and how biomonitoring can be implemented in cases of chemical incidents and if this strategy is the most efficacious tool.

S610003 Dr. C.J.W. Twenhöfel ERFRAD: Emergency response function for radiation
RIVM has a leading role in the Back-Office Radiological Information (BORI) of the Unit Planning and Advice nuclear (EPAn). In case of a large-scale nuclear or radiological emergency RIVM coordinates and contributes in the radiological environmental monitoring programme and performs model calculations providing real-time radiological analyses and prognosticated levels of radiation to the public and the environment.

Reliable and timely available quantitative risk estimates are a decisive factor in the determination of an effective countermeasure strategy. Current models use release parameters and atmospheric transport models of radioactive material driven by numerical weather prediction data from meteorological services. Input parameters of these models have large uncertainty due to the real-time requirement of the calculation. Most of the model inputs are therefore uncertain and based on expert judgment.

The ERFRAD project designed methods to improve the output for prognosticated dose levels using a data assimilation technique and introduced methods for uncertainty analyses.

For the determination of contamination, e.g. after a radioactive plume passage, statistical methods using Kriging methods are developed to automatically generate spatial maps based on the fixed radioactivity measuring network and mobile measurements from field teams.

During a release the atmospheric transport calculations were greatly improved by adding the results from the radiological measuring networks and environmental surveillance programs. As the accident evolves, radiological measurements become available and a much improved analyses can be delivered. We successfully implemented a particle filter, providing data assimilation capability of the RIVM dispersion model. At the same time this method could also provide uncertainty estimates to the model output. The results look promising and the method will be introduced.

S609002 Drs.ing. N.J.C van Belle From subacute to acute response
To protect the health of exposed citizens after severe incidents like spills and fires a realistic risk assessment is essential. It is important to restrict the consequences of air pollutants of the first phase.

In this project we focused on new sampling and analysis strategies to research the concentration of air pollutants in the acute phase of an incident. Two completely new sampling and analysis methods for environmental monitoring have been developed. These measurements have become operational and already proved to be useful during large incidents (e.g. the chemical fire in

Moerdijk). First responders and local authorities have experienced them as very useful.

Early, reliable information of the consequences of an incident reduces the impact of an accident on public health and the environment. Moreover, the results of ACUTE contributed to a substantial reduction of the response time necessary for deployment of the RIVM Environmental Incident Service with 50% or more.

S609150 Dr.ir. L. Grievink Health 10 years post disaster in Enschede
Insight in long-term (mental) health effects after a disaster exposure is highly relevant for governmental and local post-disaster health policy.

This project described the fourth health survey of the Enschede fireworks disaster 10 years post-disaster (13 May 2000) and is part of a follow-up study with prior measurements at 2-3 weeks, 18 months and 4 years post-disaster. This project contributed to (inter)national scientific knowledge of the long-term health effects, because this is the first international study following survivors for a long time and with such an early start. Persistent health symptoms (anxiety and sleeping problems) are found in 4-7% of the affected residents. About 10% of the residents with severe symptoms 2-3 weeks post-disaster had persistent health symptoms after 10 years. Measurement of early, specific disaster experiences predicting persistent health problems shows that survivors with a high level of disaster experiences (such as sustained injury, feeling intense anxiety) are at risk for developing persistent symptoms.

Since this is the first study of its kind, future studies need to confirm our results, before including specific disaster experiences as a regular part of a rapid assessment after disasters.

S660001 Prof.dr. J Meulenbelt Research cooperation in human toxicology
In case of intoxications with neurotoxic compounds, like drugs of abuse and psychopharmaceutical drugs, the National Poisons Information Centre (NVIC) can support health care workers with information about risks and adequate interventions.

Especially if intoxication of a combination of compounds has taken place, the drugs can interact with the same kind of neurotransmission. Individual vulnerability can be caused by differences in the way the body copes with the drugs. Therefore more insight in the individual susceptibility of exposure and the mechanism involved is necessary.
The effects of drugs of abuse on the dopaminergic system in the brain are investigated because this system is important in case of intoxications with drugs of abuse. The metabolism of MDMA (Ecstasy) was studied, in relation to increased liver cell toxicity and a higher risk of intoxication.

In close cooperation with the Institute for Risk Assessment Sciences of the Utrecht University (IRAS) much more insight in the mechanisms involved is gained, useful for the daily clinical toxicological practice of poisons information supply.

4 Theme Infectious diseases (INF)

4.1 INF objectives

The theme includes research into questions ranging from genetic characteristics of infectious agents to effective epidemiological interventions. Food safety issues are relevant as well. Research within this theme will help reinforce RIVM's expertise in areas such as immunology, vaccination and genetics. Given RIVM's task to coordinate the prevention and control of infectious diseases, effect studies and modelling are also highly important.

Programmes
Research projects in this theme are grouped into three programmes:

- Modelling;
- Immunology;
- Genomics.

4.2 Summarised outcome of INF

The 'Infectious diseases' projects have led to increased knowledge on the fields of mathematical modelling, genomics and immunology. Nineteen projects have been carried out. Twelve projects are still continuing in 2011 and beyond. The results of most projects are mentioned, even if they are not finished yet. Only four projects that started in 2009 and 2010 are not discussed. All project titles are mentioned in Appendix 1.

Modelling
The development of mathematical modelling is extremely relevant for the control of infectious diseases. Modelling can be used to estimate the risk of infectious diseases in certain populations, in relation to different intervention strategies.
The construction of mathematical modelling is still in full development. The results of the projects are promising. Actually, the outcome has already proven its value for policy development. An example was the new flu, which appeared in 2009. Preliminary results were used directly to take decision in control measures. The results of another project contributed to knowledge on using molecular data in mathematical modelling to increase our understanding of transmission and dynamics of infectious diseases e.g. hepatitis B. Also the significance of participation rate in screening programmes for chlamydia has been established, affecting the effectivity of the screening. Furthermore, the transfer of patients between hospitals appears to be capable of explaining much of MSRA infections in those hospitals. This knowledge may contribute to the prevention and control of MRSA. Knowledge on pathogens due to tick bites, e.g. causing Lyme disease, has grown. This is very important because much of the exact origin and control of these complicated and threatening diseases are still unknown.

Immunology
The response of individuals to infectious agents determines to a certain extent the morbidity and mortality of these diseases. Immunity is being raised by exposure to infectious agents or (cellular or a-cellular) vaccines. These immunological reactions are complicated and differ from individual to individual. The results of the SOR projects contributed to knowledge and understanding of

the immunological reactions, important for designing immunisation programmes and for diagnosis and treatment of infectious diseases. For instance, more knowledge of the role of hereditary factors in the immune response of children to 'wheezing' has been determined, understanding of 'memory immunity' has increased, and a contribution has been made to the development of serological diagnostic tests for zoonotic helminth infections. The latter is relevant because of the assumption that helminths modulate the host immune response and affect allergies. In general, with the results of the SOR projects, the toolbox needed to assess state-of-the-art parameters of vaccines–induced and infection-induced immunity has been modernised.

Genomics
Genetic markers of pathogens may help clarifying trends in infectious diseases. When this theme started in 2007 sequencing of the whole genome of (micro) organisms was quite innovative. The results of the SOR projects have contributed to the regular use of sequencing in disease control. Much knowledge has been acquired on (changes in) different pathogens. This helps e.g. to fight tuberculosis and whooping coughs, which are still a worldwide threat. New information on methods to reduce infectivity of norovirus and MRSA appeared to be also applicable to other kinds of viruses.

4.3 INF project results

In Appendix 2 an internetlink to the full list of publications is provided. The list will be updated on a regular basis. The project numbers are mentioned below and in the list of publications.

S210023 Dr. H. Grundmann Modelling the future of MRSA in the Netherlands
Antimicrobial resistance (AMR), such as MRSA (Methicillin-Resistant Staphylococcus aureus), is regarded as one of the major health threats. Most of the MRSA infections are acquired in health care settings (hospitals and nurse homes) and are frequently reintroduced. The dynamic expansion hits mostly vulnerable, older and chronically ill people. By using mathematical models based on the health care utilisation patterns in all hospitals in the Netherlands, a solid and quantitative analysis of the dispersal of MRSA in space and in time is made to understand the dispersal dynamics.

Significant correlations between the position of hospitals and the observed rates of infections were demonstrated. This makes it likely that the amount and speed with which AMR pathogens disperse at national level crucially depends on the amount of patients who move between hospitals. Since patient referrals follow established patterns inherent to a hierarchically organised health care system, tertiary care (university) hospitals will have higher levels of hospital-acquired infections because of their central position in the health care system.

By using data from the National Medical Registration, control strategies and the search and destroy approach can be put in an epidemical context and their cost-effectiveness can be estimated.

S210036 Dr. J. Wallinga Tracking emerging epidemics
During an emerging epidemic of a new infectious disease, such as the SARS outbreak in 2003 or the influenza A (H1N1)v pandemic in 2009, it is essential to have reliable estimates of key epidemiological characteristics of the new infection. These characteristics can be used to anticipate what might happen if no control measures are implemented, to estimate how much control effort is

required to stop transmission, and to suggest which groups should be targeted for control.

The key question during the project was: which groups in the population should be targeted for control, if we want to have the largest impact with a limited amount of control measures? The answer to this question is that, if the control measure is *school closure*, the group with the highest risk of infection *per capita* should be targeted for control. If the control measure is *vaccination*, the group with the highest risk of infection *per susceptible* should be targeted for control.

The findings are highly relevant for deciding which observables should be monitored during the early phase of an epidemic: the standard epidemiological risk measures such as group-specific incidence of infection (per capita risk of infection) and force of infection (per susceptible risk of infection) are directly highly informative for decisions on allocation of a limited amount of control measures. So there is no need to know the detailed contact structure of the population.

This means simple solutions to a complex problem. The data needed for control measures during an outbreak are straightforward and the required data are relatively simple to obtain.

S210046 Dr. J. Wallinga Epidemic modelling of molecular data
The effect of vaccination programmes on transmission of infectious diseases is usually assessed by monitoring programmes that rely on notifications of symptomatic illness. For monitoring of infectious diseases with a high proportion of asymptomatic cases or a low reporting rate, molecular sequence data combined with modern coalescent-based techniques offer a complementary tool to assess transmission.

Here, we investigated the added value of using viral sequence data to monitor a vaccination programme that was targeted against hepatitis B virus in men who have sex with men, in Amsterdam. The incidence in this target group was low, as estimated from the notifications of acute infections with hepatitis B virus. Therefore, there was insufficient power to show a statistically significant change in incidence. In contrast, the genetic diversity, as estimated from the viral sequence collected from the target group, revealed a marked decrease after vaccination had been introduced. Taken together, the findings suggest that introduction of vaccination coincided with a change in the target group toward behaviour with a higher risk of infection.

This will argue that molecular sequence data provide a powerful additional monitoring instrument, next to conventional case registration, for assessing the impact of vaccination.

S210056 Dr. M.E.E. Kretzschmar Chlamydia positivity and prevalence
For evaluating the effectiveness of large scale screening programmes for genital Chlamydia trachomatis (CT) infection like the Chlamydia Screening Implementation (CSI), it is important to understand the relationship between the numbers of persons tested positive in the screening and the population prevalence of infection. This relationship is not straightforward, since the participation in the screening may vary with time and target population.

To gain insight into that relationship, and how it might influence our perception of the effects of long term population based screening, a dynamic transmission

model was developed that simulates the transmission of chlamydia infection in a heterosexual population. The model describes the formation and separation of sexual partnerships and disease transmission within partnerships. Parameters are estimated from sexual behaviour surveys conducted in the Netherlands. The model is calibrated based on earlier prevalence studies of chlamydia. Using the model various screening implementation strategies can now be analysed, and their effectiveness in reducing chlamydia prevalence can be compared. A major result is that participation rates and how they develop over a sequence of screening rounds seem to be the key to effectiveness of the programme. Only if regular and repeated participation in screening can be achieved, population based screening will have any lasting effects.

Depending on participation rates and the distribution of infection in the population, annual screening might not be more effective than screening at longer time intervals. Incidence estimates from the model are used as input for a cost-effectiveness analysis of a national screening programme as piloted in CSI. In this way, the results from this project will contribute to a policy decision about the roll out of chlamydia screening on a national level.

S230426 Dr A.M. Buisman Memory immunity
Periodic measurements of population immunity learn that both vaccine-induced and naturally-acquired immunity can wane. Waning immunity is currently mostly studied by assessing antibody titres. However, the role of cellular immunity in protection against infectious diseases is also very important. Knowledge of the persistence of memory immunity induced by vaccines leads to more sustained long-term protection in the population.

RIVM started to investigate cellular memory immunity against infectious diseases and focused on whooping cough (pertussis). Apart from the induction of memory B-cells upon vaccination, the induction of helper T-cells (Th), the regulation of the balance between protection, allergy and auto-immunity is very important. In 2005 there was a major change in the national vaccination programme: the whole cell pertussis vaccine (wP) was replaced by the acellular pertussis (aP) vaccine. After vaccination with aP antibody titers are higher but also wane to undetectable levels relatively fast. Analysis of T-cell responses shows some possible important disadvantages of the switch from the wP to the aP vaccine. These responses might be associated with allergic responses and an increase in the incidence of severe local side effects. The aP booster vaccination in 4-years old children induced a higher level of Immunoglobulin E (IgE) antibodies, which is also correlated to allergy. The second pertussis booster vaccination in 9-years old children (initially vaccinated with wP) shows good B-cells and antibody responses. A continuing collaboration with European partners on memory responses against pertussis and changes in vaccination schedules between different countries will add even more useful information.

All these results may lead to the decision to lower the dose of the preschool booster vaccination and eventually to major adaptations in the vaccination schedule, based upon an (inter)national evaluation and perspective.

S230166 Dr. B. Pinelli Ortiz Zoonotic helminths and allergy
In the Netherlands, different animals are infected with worms (helminths) that can also infect humans. Evidence suggests that helminths modulate the host immune response and affect allergies.

The aim of this project was to characterise the effect of helminths on the immune response with particular interest on the effect on allergic asthma. Different helminth species are studied in order to get a better insight into which worms make allergy worse and which actually protect against allergy. Results so far indicate that while *Toxocara canis* makes allergy worse, *Trichinella spiralis* reduces allergic asthma in mice. The induction of specific regulatory T-cells during the chronic phase of an infection appears to be the mechanism by which *T. spiralis* reduces allergic asthma. These T-cells are also induced *in vitro* when dendritic cells have previously been incubated with these helminth antigens. These findings are relevant since antigens from *T. spiralis* could be used in preventing or treating allergic asthma in man.

During the studies above mentioned, new *in vitro* and *in vivo* models have been developed to study the effect of helminths and their antigens on the immune response. In addition to these models a new assay for the serodiagnosis of human trichinellosis has become available. This assay may improve the routine diagnosis of this disease worldwide.

S230406 Dr. C.M. Janssen Host response to respiratoir syncitial virus
RSV is the most frequent cause of severe respiratory tract infections in young children. About 1-3% of all infants are hospitalised because of a serious RSV infection. It is a major health problem in children. About 50% of the children will have lasting problems with wheezing respiration (post- bronchiolitis wheeze). So, identification of the factors that cause a self-limiting disease versus the necessity of hospitalisation, and occurrence of post-bronchiolitis wheeze is important.

In general infectious diseases are caused by the complex interaction between pathogens and their hosts. Traditional studies of human infectious diseases have focused on pathogen properties. New technical developments make it possible to study the role of the molecular basis of host-genetic and biological factors in the response to RSV.

In murine studies ‘natural immunity’ to RSV infection was compared with vaccine-induced disease. Both primary infection and vaccination protected against RSV challenge. However the gene expression was clearly different. Strong innate response, in the absence of viral replication but in the presence of Th2 gene expression, seems to be responsible for the enhanced pathology found in lungs. This is important for future vaccine development.
Human studies learned that genetic factors also contribute to susceptibility to RSV bronchilitis. Genes involved in innate immunity determine susceptibility to severe disease. Proteins in nasal aspirates of infants with different disease severity were used to identify markers associated with severe disease and with post-bronchiolitis wheeze.

Together these data may enable development of a model to predict which children will get long-term problems.

S230416 Dr R.S. van Binnendijk Immune pathways in vaccination
Vaccination is a key component in the elimination strategy for measles. Nevertheless measles outbreaks are known to occur even in highly vaccinated populations. Detection of virus-specific serum anti-bodies learns that infection-induced immunity is often more robust than vaccination-induced immunity. Periodic measurements of population immunity are used to monitor eradication and waning immunity, but it is unclear what makes a population at risk for

measles outbreaks. It is therefore important to know about the induction of the response of the immune system by vaccines and the cellular and genetic basis of the response.

We showed that a strong basis for cell-mediated immunity exists in the majority of measles vaccinated persons who were considered to be at risk on the basis of a routine antibody determination. By using a combination of improved virological and immunological techniques and modern genomics techniques, RIVM has designed a model to get better insight in the effectiveness of current vaccines and vaccination strategies for the elimination of measles. Immunoassays and isolation procedures were not only developed for measles, but also for other vaccine-preventable diseases. These can be used to measure if persons that are (serum) antibody negative, still have immune cells in the circulation.

So the toolbox needed to assess state-of-the-art parameters of vaccine-induced immunity is modernised. This design helps to expand the knowledge base of RIVM on vaccine-related immunology and has shown to be of use for different infectious diseases.

S230136 Dr. D. van Soolingen Whole genome analysis of M. tuberculosis
Tuberculosis is still one of the most important infectious diseases worldwide and the resistance against anti-tuberculosis drugs is increasing. The Beijing genotype of the causative agent (*Mycobacterium tuberculosis)* is significantly associated with resistance in many areas, including Europe. Moreover, Beijing strains are emerging. An important question is when the Beijing genotype strains started spreading and how clonal Beijing strains from various geographic areas are.

From the results of whole genome sequencing it can be concluded that the typical Beijing strains are highly clonal throughout the world and represent the majority of the circulating strains. Moreover, 53 mutations determine the difference of these typical and emerging Beijing strains in comparison to other branches of this genotype family. Interestingly, the majority of these characteristic mutations have been traced in genes of the regulatory network of typical Beijing strains and it is conceivable they have a major influence on the overall expression. Recently it was also discovered that Beijing strains have a much higher mutation frequency when exposed to particular anti-tuberculosis drugs and, hence, have a higher ability to generate resistant mutants.

These findings are important for understanding the dynamics of tuberculosis and finding new ways for prevention and control.

S230436 Dr. A.J. King Microarrays to map pertussis adaptation
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. Changes in the circulating *B.pertussis* population have been identified, over a period of 60 years. The aim of this study was to identify changes on genomic and gene expression level, the relevance of the changes and the relation with changes in pertussis (whooping cough) epidemiology.

B. pertussis seems to be influenced by changes in the vaccinated host. It is a dynamic organism that continues to evolve. In the past decade *B. pertussis* strains carrying the *ptxP3* allele are dominating the Dutch *B.pertussis* population. These strains all are characterised by a specific gene profile, with

higher expression of the virulent factor of pertussis toxin. Strains of different foreign countries show a similar development and no geographic specificity. The genome size of *B. pertussis* strains decreased progressively over the past 60 years.
The RIVM assay enables fast high quality (genome wide) comparisons of international *B. pertussis* strains.

Better knowledge of factors contributing to an increase in virulence will be of importance to influence the advice for the most effective method to prevent pertussis.

S230446 Dr. F.R. Mooi Bortedella pertussis adaptation to vaccination
In spite of widespread vaccination of young children, whooping cough (pertussis) remains an endemic disease and has resurged. Even new, acellular, vaccines have not resulted in containment of the disease. This project elucidates the causes for the persistence and resurgence of pertussis in vaccinated populations.

There is strong evidence that a group of highly related (P3) strains is spreading globally and causing epidemics. In particular, the increase in pertussis incidence in adolescents and adults is associated with the emergence of P3 strains. RIVM research suggests that P3 strains harbour adaptations which suppress host defences, which may particularly enhance transmission when vaccine immunity has waned. The genome sequences of six strains were determined to identify adaptive mutations in P3 strains. Twenty six point mutations were found to be specific for P3 strains and many of these were located in genes involved in regulation and virulence. Also evidence was found that gene activation and inactivation was important for adaptation. In conclusion, this study suggests that small mutations and gene (in) activation allow B. pertussis to adapt, explaining its ability to persist in the face of vaccination.

The genome sequences allowed us to develop a novel typing system for B. pertussis. Reliable methods to type bacterial pathogens are an important tool in infectious disease control. This method will be used to identify newly emerged successful strains and may serve as an early warning system for epidemics. This project will provide a rational basis for the adaptation of vaccines or vaccination programs.

S330116 Dr. H. Sprong Ticks: Trojan horses with new surprises
The incidence of Lyme disease is on the rise, most likely due to an increase in tick bites. Apart from the Lyme-spirochete, other potential pathogens, among which *Rickettsia helvetica*, are present in ticks. The question was whether exposure to Rickettsia through tick-bites constitutes a risk to human health.

Remarkably, it appeared that not all Rickettsia-seropositive Dutch patients recall a tick bite. Humans do not develop overt and acute symptoms upon exposure to *R. helvetica* trough tick bites. However, *R. helvetica* may cause chronic infections in humans. Investigations revealed that *R. helvetica* is as prevalent and as widely distributed as the Lyme-spirochete in the Netherlands. Moreover, *R. felis* was discovered for the first time in cat fleas in the Netherlands.

These findings imply that the human population is not only exposed to *R. helvetica* via ticks but also to *R. felis* via cats and their fleas. New research is unravelling the aetiology of *R. helvetica*. Tools, developed during this study, are already implemented in clinical and international settings. As first institute RIVM has tested English ticks on Rickettsia. The Amsterdam Academic Medical Centre

(AMC) could be supported by molecular diagnostic of patients, suspicious for a Rickettsia infection from Africa.

S230156 Dr. E. Duizer Transmission intervention strategies
In the Netherlands noroviruses (NoV) are the main cause of gastroenteritis each year. NoV are shed via vomit or faeces of infected persons. The virus can be transmitted from one person to another via direct contact or indirectly via contaminated food, water or surfaces. To reduce the burden of NoV infections science based protocols for transmission intervention are presented. These protocols should not only be effective against NoV, but preferably also against other viruses that may be transmitted via food or hard surfaces.

Therefore, inactivation experiments were performed with different enteric and respiratory viruses. We found that heating food to at least 73 °C for 3 minutes sufficiently inactivated the virus. In another experiment the effect of a method (based on vaporised hydrogen peroxide) used in hospitals to decontaminate rooms after contamination with MRSA was tested for virucidal activity. This method works welln in reducing infectivity of all the viruses tested, including norovirus, rotavirus and influenza virus. In conclusion, hospital rooms contaminated with different viruses can be decontaminated by this method. The LCI (national coordination of infectious disease control) protocols are tested now for their effectiveness as intervention measures during NoV outbreaks. The virucidal effects of commercially available hand disinfectants are being evaluated.

This project is being performed in close cooperation with Wageningen University. Although the project is not yet finished, it has already provided the scientific rationale underlying the vaporised hydrogen peroxide intervention strategy and received clinical interest.

5 Theme Chronic diseases, intervention and lifestyle (CIL)

5.1 CIL objectives

Chronic diseases and lifestyle changes constitute growing problems and require policy-making at local, national and international levels. Available knowledge about preventive interventions should be implemented more fully, and new types of prevention should be developed. High-risk groups need to be identified early on, and receive special attention. Increasingly, links between life styles and health are being debated, and citizens are encouraged to adjust their behaviours. Food quality, obesity, diabetes, cancer, medical screening, and quality of life are just a few of the issues that are more and more coming together, and the trend will most likely continue. Growing expertise on these interfaces at RIVM will be needed.

Programmes
Research projects in this theme are grouped into four programmes:

- Modelling chronic diseases;
- Healthy ageing;
- Quality of care;
- Economic evaluations.

Besides, five projects on different subjects, which did not fit into the four programmes, have been executed.

5.2 Summarised outcome of CIL

The ‘Chronic diseases, lifestyle and intervention’ projects have led to an increased knowledge on the fields of modelling, healthy ageing and quality of care. Seventeen projects have been carried out. Seven projects are still continuing in 2011 and beyond. The results of most projects are mentioned, even if they are not finished yet. All project titles are mentioned in Appendix 1.

Modelling chronic diseases
Modelling tools are of utmost importance to answer the questions of RIVM’s principals. Instrumentation is necessary to provide quick answers to complicated questions. This instrumentation permanently must be upgraded, to meet the changing needs of the principals. The RIVM Chronic Disease Model (CDM) plays an indispensable role in much of RIVM’s work. Two projects contributed to RIVM chronic diseases modelling skills. The CDM has enabled the evaluation of socio-economic status aspects. Furthermore, the model has been adapted by making a user-friendly software version. This enlarges the potential use of the model greatly, and simultaneously incorporated RIVM’s modelling skills into an international setting.

The potential of public health modelling has been demonstrated by the project on cardiovascular diseases and diabetes. A contribution has been made to knowledge on lifestyle factors and risk factors, which is important to the improvement of prevention programmes. The results have already contributed to new guidelines on treatment of cardiovascular diseases in the Netherlands. Because nutrients, additives and food items can cause both health benefits and health risks, policymakers need a method that quantifies health gains or losses by changes in dietary intake. Through SOR, RIVM participated in two EU

projects, in which a method and a web-based tool to assess benefit-risk questions in foods were developed.

Healthy ageing
Healthy ageing is a societal issue of increasing relevance. Important information on the interrelationship between healthy ageing on the one hand, and overweight or underweight on the other hand has been acquired. Although many people are aware of the risks of overweight, underweight among elderly is also a serious problem, because it appears to be a significant risk factor for premature death. This information is important for the formulation of clinical guidelines and will also be incorporated in the above mentioned chronic disease model. On the molecular level, knowledge on the effect of diet has been obtained, which helps to understand how healthy ageing can be influenced by gene diet interactions.

Quality of care
Every penny can be spent only once, so information on quality of care together with cost implications is needed to improve the quality of healthcare. Firstly, adequate performance indicators are needed, which means that they are representative of the underlying quality of the healthcare system. More knowledge on this topic has been gained, which reinforces the need of empirical testing theoretical relationships. Otherwise, indicators may not be as useful as hypothesised. Furthermore, information has been obtained on the relationship between health of elderly and health expenditures, based on trends in health and on disabilities connected to chronic diseases. This information is important to forecasting health status and future policy decisions, leading to more explicit decision making.

Economic evaluations
It is evident that economic evaluations are important for decision making, so adequate methods are crucial and need improvement constantly. A toolkit has been developed facilitating the incorporation of future unrelated health care costs in economic evaluations. Furthermore, new methods for communication and valuation of uncertainties of outcomes in economic evaluations have been developed. These improve the existing instrumentation and its usefulness for policymakers significantly.

Other
More knowledge has been acquired on a range of topics related to chronic diseases. RIVM has access to several cohorts, which are important for epidemiological studies on the relationship between lifestyle and the development of chronic diseases. New knowledge has been obtained by performing cohort studies on the relationship between lifestyle factors and chronic diseases and cancer. Children were a specific target group in one study, because childhood lifestyle lays the foundation of the development of chronic diseases later in life. Remarkable results came from a study on common chronic health problems in children, a problem that deserves more attention in future research, because chronic health problems in children appeared to be widespread and can seriously affect their development.

Adequate data at low costs are important in all epidemiological public health studies. It was concluded that it is possible to obtain reliable data on health of children by using questionnaires completed by parents. This means a large saving compared to obtaining data by professionals. Furthermore a step forward has been made in getting valid data on the occurrence of diseases from general practice registries.

5.3 CIL project results

In Appendix 2 an internetlink to the full list of publications is provided. The list will be updated on a regular basis. The project numbers are mentioned below and in the list of publications.

S260146 Dr.ir. W.M.M. Verschuren Primary prevention research on cardiovascular diseases and diabetes
This project aims to increase knowledge on modifiable risk factors for cardiovascular diseases (CVD) and type 2 diabetes (DM), relevant for the Dutch situation. Both diseases are an important public health problem, they share common risk factors, and DM itself is a risk factor for CVD. This project has harvested the RIVM population based studies (Doetinchem cohort and the MORGEN-EPIC cohort).

This project has shown that a higher intake of both fruit and vegetable lowers CVD risk, while increasing consumption of fatty fish reduces the risk of only fatal CVD. Moderate alcohol consumption further reduces the risk of DM. Overweight/obesity is an important determinant of CVD and DM. Especially in young persons, weight gain increases the risk of DM. The most recent level of the Body Mass Index (BMI) is the strongest predictor of DM, meaning that weight history does not have to be taken into account. Physical activity (cycling and sports) prevents CVD, and also prevents becoming overweight. A good night's sleep is also important. Those with a short sleep duration who do not rise rested in the morning are at increased risk for CVD.

Important results have been obtained in the field of cardiovascular risk management. The (international) risk prediction formulas currently used by general practitioners overestimate risk for CVD mortality in the Dutch situation. The impact of changing from predicting mortality to predicting morbidity and mortality is presently being studied.
This project has also contributed to international activities on determinants of CVD.

S210116 Prof.dr. H.C. Boshuizen Adaptable chronic diseases modelling
The RIVM Chronic Disease Model (CDM) integrates information of a large number of diseases and risk factors together with demographic information. This makes it possible to calculate the burden of diseases in the Netherlands and to evaluate the effects and costs of health policies and preventive interventions. The RIVM CDM is applied regularly for these aims in the Netherlands.

To facilitate the use of CDM-methodology by other researchers, both international and national, a user-friendly software version of a similar model has been developed in cooperation with Erasmus University. This software tool, DYNAMO-HIA, built by RIVM, is meant for estimating the health impact of policies. Its user does not need any programming skills. The downloadable model contains datasets for use in different EU countries compiled by international partners of the DYNAMO-HIA project.

Furthermore a micro-simulation tool has been developed. The classical CDM is limited in the type of questions it can answer. Micro-simulation is a method in which a large number of lives are simulated. This is more flexible because in micro-simulation factors can be manipulated on the level of the individual, while

in the classical CDM they can only be manipulated on the level of population groups.

The micro-simulation tool is designed to be flexible and the user can change some pre-specified parts of code in order to adapt the model to new requirements. This makes it possible to compare the effects and cost of prevention with that of treatment, or to compare treatment options.

S260166 Dr. P.C.A. Droomers Modelling socio-economic status disparities in health
Health inequalities in the Netherlands are enormous. There is a difference between high educated and lower educated people in life expectancy and healthy life expectancy of respectively four and fifteen years. The Dutch government has in 2001 adopted a target to increase the healthy life expectancy of the lowest educated groups with 3 years by the year 2020.

The RIVM Chronic Disease Model (CDM) is able to forecast the effects of interventions and health policies but can only evaluate the average situation in the population. In case of smoking, however, a distinction between socio-economic groups could already be made. We have now developed an extended version of CDM enabling the evaluation of the impact on socio-economic health differences. This socio-economic model is filled with data from national public health surveys as well as general practice registrations. The public health surveys provide information on socio-economic differences in smoking and overweight. The general practice registration provides information on the incidence and prevalence of six chronic conditions, i.e. acute myocardial infarct, stroke, heart failure, low back pain, diabetes, and chronic obstructive pulmonary disease (COPD). Socio-economic status is indicated by educational level. Information on the distribution as well as the development of the educational level of the Dutch population is obtained from Statistics Netherlands. Using this socio-economic CDM differences in life expectancy and expected lifetime with a chronic condition between socio-economic groups can be calculated.

Examples of this type of analysis suggest that prevention of chronic conditions should not only focus on lower educational groups, but also target the higher educational groups given their higher expected years to live with the chronic conditions as mentioned above

S350040 Dr.ir. J. Hoekstra Modelling health effects of nutrition
Our food should be safe and healthy. However, foods may include benefits as well as risks. For example eating fish lowers the risk of cardiac death but mercury in fish affects the neurological development of newborns; folic acid will reduce the number of babies born with a neural tube effect but may also increase the incidence of colon cancer in the population. Because nutrients, additives and food items can cause both health benefits and health risks policymakers need a method that quantifies health gains or losses by changes in dietary intake.

The RIVM participated in two EU projects, BRAFO and QALIBRA. BRAFO developed a method to assess these benefit-risk questions. In QALIBRA a web-based tool is designed to quantitatively assess benefits and risks in foods. This tool can be used in the BRAFO approach. The method and models are of great importance in harmonising the risk-benefit approaches within the EU.
Using the expertise of the RIVM and the developed tools policymakers are better able to balance risk and benefits of food policies and interventions such as

making recommendations, fortifying foods and reformulating food products or production methods.

S206156 Dr.ir. W.J.E. Bemelmans Healthy ageing: overweight/underweight
With the ageing of the population it is important to gain insight in determinants of health at older age. It is well-known that the prevalence of overweight increases and overweight is associated with several diseases, such as cardiovascular diseases, diabetes, and certain types of cancer and disorders of the locomotor apparatus. So it is highly relevant to study the interrelationship between ‘healthy ageing’ and ‘overweight/underweight’.

A meta-analysis (with data from more than 58,000 elderly) about the associations between waist circumference/BMI and disease specific mortality in 65-75 year olds was finished. The results clearly confirmed that mortality within 5 years among elderly having underweight is twice as high. Furthermore we found that an increased waist circumference is a better indicator to assess increased risks in case of overweight than BMI. A two fold increased mortality risk for cardiovascular diseases were observed among elderly having a waist circumference of 119 cm (men) or 110 cm (women). These last results can be used in clinical guidelines for treating obesity.

The combination of prevalence rates of underweight and increased waist circumference with the increased mortality risks makes it possible to decide which target population can profit most from interventions. Besides the direct clinical relevance, the results of the project will contribute to improved quality of calculations with the Chronic Disease Model.

S340020 Dr. M.E.T. Dollé Healthy ageing: gene-diet interactions
An important issue for public health policies worldwide is healthy ageing, with the focus on the increase of healthy years. Preventive measures must lead to a decrease of severity and to delay the time of onset of chronic diseases as cardiovascular diseases, diabetes, obesity and cancer. Both diet and genetic composition influence the susceptibility to these chronic diseases and ageing itself. It is fundamental to understand the relation between molecular mechanisms and diet that underlie ageing and the already mentioned chronic diseases.

From studies in mice we learned that different enzymatic deficiencies accentuate different aspects of ageing. A mouse model with a short life span (of about 20 weeks) was extensively characterised and shown to have similar multiple signs and symptoms of ageing, compared to wild type mice living for 2 to 3 years. These DNA-repair-deficient-mice can be used as a short time model to test ageing intervention strategies, and to identify biomarkers for specific ageing related symptoms. As proof-of-the-principle, diet restriction (a well known intervention to slow the ageing process in many species) was applied. In these mice a 30% diet restriction resulted in an unprecedented doubling of their life span. This finding reinforces the relation between aging and metabolism and suggests the model can be used to test other intervention strategies as a cost and time effective alternative to wild type mice.

At the same time, common genetic variations in the general Dutch population were examined regarding their influence on various risk factors of metabolic syndrome and the modulation by diet and lifestyle. However, the complexicity and the small effects of thes common genetic variations prevented the identification of clear gene-diet interations, modulation health predictors in the

human studies. New studies, aimed at the identification and application of biomarkers to monitor the ageing process in human populations, have been intiated.

This model may prove its utility since, the complexity and the small effects of common genetic variations in the general population have so far prevented the identification of clear gene-diet interactions modulating health predictors in human studies.

S260116 Prof.dr. G.P. Westert Health system performance: Netherlands and Canada
In the last few years, different countries were motivated to reform various aspects of their healthcare systems with the aim of reducing costs while improving quality. Quality improvement begins with measuring performance. Performance indicators used to measure the quality of healthcare can be classified into structure, process, and outcome indicators (SPO, the Donabedian triad). However, it is often not clear whether the selected performance indicators are representative of the underlying quality of the healthcare system.

This project concentrated on the effectiveness-domain of healthcare, and explored the relationships between indicators in the Donabedian triad using ‘case studies’. Each study looked at the validity of an indicator, and its presumed theoretical relationships. The results obtained reinforced the need to test these relationships empirically. The need for empiricism extends beyond direct relationships with outcomes and also includes groups of indicators presumed to measure the same aspect of care. In examining the practical applications for indicators one can distinguish between scientific and policy relevance. A number of scientific findings can indeed be translated into policy platforms, but sometimes (the most) effective policies may only be determined by waiting for further evidence.

Healthcare is an interconnected process with limited resources available. An emphasis on understanding the relationships between indicators not only informs future research, but also reassures that the inferences from observed performance are correct.

S270116 Dr. C.H. van Gool Are diseases becoming less disabling?
With the ageing of the population, more people will have chronic diseases. Reduction of disabilities, accompanying diseases, will lead to a healthier and more active elderly population, and also to the reduction of the demands for long-term care. The healthy life expectancy has become an important indicator to monitor population health.

This project is the first study on trends in diseases, activity limitations and their interrelationships in the Netherlands, based on large amounts of original data from the past two decades. To get a univocal insight in and explanation of the trends of disabilities in the Netherlands a harmonised database with original data gathered on health, disease, and demographic characteristics, was planned. The analysis of the heterogeneous, both cross-sectional and longitudinal collected data, made a custom-built meta-analytic strategy necessary. Using *overall* results we found no declines in activity limitations in the Dutch older population over the period 1990-2007. The hypothesis that diseases became less disabling over this period, however, was supported using the results on activity limitation data as assessed with a specific instrument.

Putting the results into public health context, the empirical results have contributed to the awareness that in the Netherlands the prevalence rates of chronic diseases are on the rise, but at the same time people do not become disabled more than before. Apparently, there is more to health than the absence of illness.

S270166 Dr. J. Polder Healthy ageing and health care expenditure
Ageing of the population has an important impact on health expenditure in the Netherlands. It matters, however, whether ageing will add healthy or unhealthy years. In this project the different determinants of health expenditure will be disentangled, comprising a variety of influences with a focus on population health.
Better knowledge about the relation between the health of the (future) elderly and health expenditures enables us to enhance traditional scenarios of future health care expenditures with the influence of trends in population health. So we demonstrate that living longer in good health, especially without disability, will not increase a person's life time health expenditure. We study also the dynamic influence of changing health as a result of effective treatment. Since this project started later, we only have some preliminary results that show that health care, also at higher ages, does improve the health status of people and contribute to some postponement of health care needs. Furthermore we try to get some grasp on differences between people born before and after World War II. Since the baby boomers will age in the near future, it is important to get some better understanding of their specific health needs.

The results are important for policymakers who are interested in the several ways that ageing will influence health expenditure, and who are willing to develop some scenarios for the health care sector to be prepared for the health care needs of our future elderly.

S260176 Dr. T.L. Feenstra Communicating uncertainty in economic evaluations
Useful support of public health policy requires a clear communication about the (un-)certainty of outcomes in economic evaluations and insight into their implications for decision making. This project tested the usefulness of two methods: the real options approach and the value of information analysis, applying them to four cases.

Results of the testing indicate that uncertainty around outcomes is especially important if decision makers allocate relatively small budgets over a limited set of interventions. Choosing one intervention may then prohibit the full implementation of another intervention. A specific communication tool shows the best solutions to such allocation tasks for varying attitudes towards risk in a single table. The real options approach uses analogies to financial options to value the flexibility that is lost once irreversible investments are done, e.g. in a new health care intervention.
Cases were the stockpiling of antiviral drugs, and the (conditional) reimbursement of antifungal drugs. Loss aversion towards the negative health consequences explains why investment will be higher than conventional cost benefit analysis would suggest.

Value of information analysis (VOI) evaluates the value of doing additional research before taking a decision. It considers the potential impact of research outcomes on the actual decision, i.e., whether or not the intervention is cost-effective. VOI was applied to depression prevention and screening for Coeliac Disease among patients with Irritable Bowel Syndrome (IBS). The work on IBS

supported new multidisciplinary treatment guidelines and helped to determine whether all IBS patients should be screened or only specific subtypes. The work on depression prevention supports better informed decisions regarding opportunistic screening at GP practices for sub threshold depression and offering minimal contact psychotherapy. We found that better data on the absence from work related to depression will improve the reliability of the cost-effectiveness outcomes for this intervention.

Taken together these methods enable policymakers to better include uncertainties in their decision process.

S260186 Drs. G.A. de Wit Future unrelated medical costs
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 health economic evaluations as cost-effectiveness analysis and cost-utility analysis a subject of discussion is whether future unrelated medical care must be included or not. As first worldwide the RIVM has developed a toolkit facilitating the incorporation of future unrelated health care costs in economic evaluations. This toolkit (named PAID) contents a list of items that needs to be addressed in order to make appropriate choices on the inclusion of these costs in a standardised way. Incorporating future unrelated medical costs in economic evaluations will improve the comparability of cost-effectiveness ratios from different interventions. In general, cost-effectiveness ratios that are adjusted for future unrelated medical costs will be somewhat less favourable than unadjusted ratios. However, adjusted ratios will help policymakers to make optimal and unbiased, evidence-based decisions on the implementation of different health care and preventive technologies.

It is expected that the availability of the toolbox will be crucial in the upcoming decision to change the current guideline whether or not to include future unrelated medical costs in economic evaluation. Recently published guidelines for costing research already advocate the inclusion of future unrelated medical costs in economic evaluation studies.

S350020 Dr. H.B. Bueno de Mesquita Primary prevention research on obesity, cancer and ageing
Due to the ageing of the population the burden of chronic diseases and cancers will increase substantially. The number of cases with cancer, diabetes and obesity will rise. Primary prevention of these diseases potentially improves quality of life considerably. This project focussed on the role played by lifestyle factors like dietary and other determinants (such as physical activity, smoking, educational level) in the development of obesity and cancers. The large number of publications is remarkable. This was possible thanks to the extensive international network in which the project is embedded.

Results of epidemiological research on risk factors of chronic diseases, conducted in (international) consortia, have shown that differences in cancer risk by educational level could not always be explained by known risk factors. A larger quantity and variety in the consumption of fruit and vegetables may reduce the risk of several cancers, while smoking and consumption of red and processed meat may increase cancer risk. Higher blood levels of the good cholesterol (HDL), and of vitamin D may reduce the risk of colon cancer.

Adherence to a Mediterranean diet, lower consumption of meat and more physical activity may help to prevent weight gain.

Large-scale population studies learn that a healthier lifestyle seems to be the most important factor to prevent cancer and overweight. It is generally accepted that policies directed to a healthier lifestyle leads to substantial gain in health**.**

S270126 Dr. A.J. Schuit Knowledge transfer in public health
Although the knowledge about determinants of unhealthy lifestyles and the effectiveness of interventions is increasing, the contribution of research and development of interventions to health promotion in practice is still disappointing.
For many years the solution for this problem was sought in designing better interventions at-a-distance, and improving their top-down transfer and precise implementation in practice. Experience has shown that design and optimisation of interventions (including effectiveness research) can only partly be organised at-a-distance from practice. When an evidence based intervention is realised in practice it always differs from the original one. Hence, health promotion is largely a co-production of top down knowledge en local learning.

A new strategy proposed in this project takes this as a starting point and tries to work towards a system that facilitates the distributed actions and heterogeneous learning processes that together add up to interventions that work in local practice. To contribute to this, a system has to be realised in which the distributed actions of heterogeneous actors together lead to the most effective design pathways. The key consideration is joint learning and the way it contributes to improved practices for health. Such a strategy cannot be based on a blueprint, as the optimum approach depends on the particular situations and goals of actors, but suggestions for ‘doing better’ can be made.

In this project a method is developed to assess *if* and *how* research contributes to action. By systematically unravelling the various linkages of the design of a configuration, the method generates suggestions for improving design pathways and the co-evolving systems in which they take place, to ultimately increase the chance of societal benefit.

S260126 Dr. A.H. Wijga Lifestyle from childhood to adolescence
Childhood lifestyle and environment lay the foundation for the development of different chronic diseases such as diabetes, cardiovascular disease and asthma in the adult population. To gain insight into these processes, data from the PIAMA study (Prevention and Incidence of Asthma and Mite Allergy), a long-term follow-up cohort study with 3500 children followed from before birth (1996/1997) were used to study the influence of early-life factors on cholesterol concentrations in 8-year-old children.

The study showed that children of mothers who were overweight before pregnancy or who smoked during pregnancy and children who gained weight very rapidly in the first year of life had relatively high BMI values and (independently of BMI) relatively high HDL-to-total cholesterol ratios when they were 8 years old. Reliable measurements of children's body size and shape can be obtained from questionnaires completed by the parents because of the strong correlation between the values obtained by the parents and those obtained by professionals. Although 20% of the parents of heavy children tended to underreport their child's weight and waist circumference, there was still a good agreement in the ranking of children, which simplifies future research.

In conclusion, the PIAMA questionnaire data can validly be used in epidemiological studies on associations between measures of body size and either risk factors or health outcomes.

S260136 Dr. A.H. Wijga Chronic health problems in childhood
About 20% of all children have one or more common chronic health problems. Their conditions deserve more attention to get better insight in nature, seriousness and prevalence. In particular allergic diseases like asthma, eczema and hay fever are common. Furthermore, pain (like headaches or migraine and abdominal pain), malaise complaints and depressive symptoms make out a substantial proportion of children's and especially of teenagers' health problems. These latter problems are largely invisible for the health care system because the majority of the children do not visit the general practitioner for their complaints.

This project contributed to the report 'Chronic health problems in children in the Netherlands: an inventory of prevalence and consequences'. Two to three percent of all children (about 100,000 children) experience serious limitations in daily functioning due to their chronic health condition. Children with such health problems often have combinations of physical and psychological complaints, decreased quality of life and a higher rate of school absence. The report further contains information about prevalence, types and severity of disease, trends and groups-at-risk for chronic disease next to consequences of chronic illness in terms of quality of life, social functioning and participation in 0-18-year-olds in the Netherlands.

The available evidence is not yet sufficient to reliably estimate the consequences of children's development, their social participation, their school performance or their later well-being. However, the use of already existing data can bridge these knowledge gaps in the future.

S270146 Dr.ir. F.H.G.M. Hoeymans Validation of data from general practice registries
Governments need objective information about the health status of their inhabitants. Core indicators for describing population health are life expectancy, health expectancy, and incidence, prevalence and mortality for a selection of diseases.

Data about the occurrence of diseases can be collected by health interview surveys measuring self-reported diseases. However, in the Netherlands it is also possible and probably advantageous to use data from registries in general practice (GP), mainly because these diseases are diagnosed by doctors instead of self-reported. However, at present incidence and prevalence rates achieved from several registries differ considerably. It is not clear what causes the difference between registrations. To provide valid and useful information on the prevalence and incidence of diseases in the population, these differences must be explained. Also recommendations must be formulated about how data registered in general practice can be used in public health reporting. Recently is found that the differences between the registrations cannot be declared by population characteristics.

New investigation concerns the influence of characteristics of the general practice (for example male or female doctors, age, experience) on the morbidity outcomes of the general practice registration networks. Also the question what

defines the validity and reliability of the Dutch morbidity from registries in general practice will be answered.

6 Theme Medicines and functional foods (MFF)

6.1 MFF objectives

More and more, medicines and novel foods become intertwined, and RIVM needs to acquire more expertise in this area. Straightforward risk assessments are moving towards risk versus benefit analysis and chain approaches. Also, it is becoming more important to grasp system functions in care. Also consumer behaviour and understanding need proper attention.

Programmes
Projects within this theme are all related so no separate programmes have been identified.

6.2 Summarised outcome of MFF

The ‘Medicines and functional foods’ projects have led to increased knowledge on safety of drugs and functional foods. Nine projects have been carried out. Five projects are still continuing in 2011 and beyond. The results of most projects are mentioned, even if they are not finished yet. Two projects that started in 2009 and 2010 are not discussed. One project was terminated because it proved unfeasible. All titles are mentioned in Appendix 1.

To obtain safe medicines, adequate methods for risk analysis and risk assessment are of utmost importance. An overview of existing experience with the use of risk management tools for quality risk management in the pharmaceutical industry has been build up. Furthermore in-depth insight into the possibilities, limitations and pitfalls of several risk analysis methods has been gained. More specifically, observations were made on the possibilities of reducing costs of expensive laboratory tests to assess unbranded copies of branded medicines, within the precondition to maintained safety.

Several studies on specific medicines resulted in useful knowledge on side effects of drug use. For instance, chronic statin (cholesterol reducing medicines) use may have adverse effects on health; it may lead to Rheumatoid Arthritis as well as Systemic Lupus Erythematosus. An in vitro test has been developed that may be used to assess undesired immune response to therapeutic proteins and side effects of vaccination. Furthermore, the spin off of a study on medicines for use in children is included into a quality guideline on the pharmaceutical development of paediatric medicines.

More and more functional foods and dietary supplements are introduced to consumer markets. Especially claims, safety, efficacy and product handling of the foods and dietary supplements, in alternated or combined use with pharmaceuticals, are important. To inform consumers, professionals and policymakers a prototype of a food-pharma database has been developed. Functional foods might be interesting to replace drugs, if sufficient effectiveness can be proved. Results from one of the projects in this theme did not confirm the feasibility of replacing statines by phytosteroles.

6.3 MFF project results

In Appendix 2 an internetlink to the full list of publications is provided. The list will be updated on a regular basis. The project numbers are mentioned below and in the list of publications.

S340040 Dr.ir. R.J. Vandebriel Chronic drug use and autoimmunity
Diabetes Mellitus I, Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosis (SLE) are examples of individual autoimmune diseases. The risk to get an autoimmune-like disorder can be induced or increased by drugs use. Statins (cholesterol reducing medicines) have an effect on the immune system. The prevalence of autoimmune diseases is increasing.
To know more about the associations of long-term drug use with chronic inflammatory autoimmune diseases, the association between statin intake and autoimmune diseases was studied. From reports of spontaneous adverse drug reaction (ADR) data, indicating a relation between satins and Polymyalgia Rheumatica (PMR, a muscle disorder) and SLE, an association between reporting of PMR and SLE and statin intake is found. Results from general practitioner databases showed that RA patients were more often users of statins compared to individuals not suffering from RA, suggesting a relation between statin use and RA.

Serum analysis did not demonstrate the association of statin intake with the presence of (auto) immune markers (serum auto-antibodies).This supposes a medicine specific relationship.RA patients were more often users of statins compared to individuals not suffering from RA.

This project may indicate a reserved policy for prescription of statins in patients with low cardiovascular risk.

S350030 Dr.ing. H.J. van Kranen The food pharma interface
The interaction between pharmacology and nutrition science is on the rise. This is, amongst others, illustrated by the introduction of more and more functional foods and dietary supplements to consumers. Not only consumers, but also professionals like general practitioners, pharmacists and dieticians, need evidence based information on the food-pharma interface. Especially (health) claims, safety, efficacy and product handling of the foods and dietary supplements, in alternated or combined use with pharmaceuticals, are important.

The ‘proof-of-principle’ example throughout the project has been the modulation of cholesterol levels, being one of the important cardiovascular risk factors. Along the same principles information about other traits like bone health, obesity, brain health and ADHD can be worked out. To inform consumers, professionals and policymakers, a prototype of a food-pharma website (FPI website) has been developed. Moreover, essential ICT building blocks have been designed as well. In addition, epidemiological and experimental animal studies, were performed to gain insight into both positive and negative aspects arising from the combined intake of pharmaceuticals and functional foods.

First, the combined effects of respectively plant sterols, unsaturated fatty acids and specific dietary fibres were examined. Secondly, the behavioural interactions related to the combined intake of functional foods and statins, like drug adherence, were studied. Finally the cost-effectiveness of adding functional foods enriched with plant sterols to statin therapy in relation to the prevention of cardiovascular diseases and health care costs were evaluated. All these results will be bundled later in 2011.

S360020 Dr. M.H.N. Hoefnagel Immunogenicity of protein pharmaceuticals
Vaccination is directed at generating protective immunoreactions. Therapeutic protein medicinal products on the other hand should not induce an unwanted immune response as this may reduce or annihilate the efficacy of the therapeutic protein. For both types of products it is essential to test their immunogenic potential. Current immunogenicity testing in animal studies are generally not very relevant, firstly because their immune system differs from humans, secondly, human proteins are foreign to animals and will more likely raise an immune response and finally, immunogenicity against fully human biopharmaceuticals only develops slowly and is hard to predict from clinical studies. There is a clear need for an *in vitro* assay representative for the *in vivo* system to predict the immunogenicity of biopharmaceuticals.

RIVM has developed an *in vitro* assay using *human* immune cells (MUTZ-3 Dendritic Cells). This assay is capable to discriminate between three components of the *Haemophilus influenzae* type B vaccine (Hib) that have different immunological effects *in vivo*. This test may have great potential for measuring vaccine immunogenicity also for other vaccines and therapeutic proteins.

Because human cells are used this immunogenicity assay is more relevant than animal tests so this assay contributes to safer and more efficacious medicines and the reduction of animal testing.

S370010 Dr. D.M. Barends Riskred
Risk analysis, the systematic analysis of the potential risks of a failing product or a failing process, is nowadays a widely used procedure to reduce risks. Several methods are in use, differing in the kind of data gathered, such as expert judgment and computer simulation, and qualitative and more quantitative methods. However, in pharmacy, the application of risk analysis is still limited.

RISKRED applied several methods of risk analysis to pharmaceutical situations, to get a better knowledge of the possibilities and limitations of the several methods. A literature search on the use of risk analysis in pharmacy was performed, and one risk analysis method, Failure Mode and Effects Analysis (FMEA), was applied to a crucial laboratory test, of which the outcome could be used in court. With respect to this laboratory test, the results of that FMEA were used to make the test even more robust. On the level of knowledge of risk analysis, this FMEA provided an in depth insight in the possibilities, limitations and pitfalls of this risk analysis method, which is now also applicable to the assessment of industrial pharmaceutical situations.

This method will be used in a study on actual risks of illegal medicines to public health. On a more systematic level, RISKRED had a major impact on the general concepts of the quality of pharmaceuticals and of pharmaceutical care.

S370020 Drs. D.A. van Riet-Nales MAGIC: Manipulation and administration of medicines given to children
The range of approved medicines for use in children is limited in number, diversity, actuality and formulation design compared to those for adults. As a consequence the European Commission has prepared new legislation to increase the research, development and authorisation of medicines for use in children. More knowledge needs to be gathered about the principles of the development of age-appropriate formulations for children and if not possible, the good manipulation of adult medicines for use in children or the application of extemporaneous preparations.

As part of Magic a systematic literature review on the relationship between pharmaceutical technology aspects and patient outcomes has been published as well as a study on the availability and age-appropriateness of licensed medicines for children. Also a questionnaire study among patients on their problems with the administration and manipulation of medicines has been finalised. Currently, a patient study of the child acceptability and child preference of medicines in different forms (mini tablet, powder in sachet, suspension and syrup containing placebo medication) is running, just like a study of the volume, nature and age-appropriateness of compounded medicines for children in Dutch hospitals. Another study on the characteristics of paediatric formulations in the paediatric investigation plans is currently developed.

The spin off of this study for the European Union regulatory system is expert input into a quality guideline on the pharmaceutical development of paediatric medicines. This SOR study will be continued by funding from third parties.

S37003 Dr. D.M. Barend BIOTRHEE
Generic medicines are unbranded copies of branded medicines of which the patent has been expired. The 'gold standard' for assuring the 'appropriateness' of a generic is an *in vivo* bioequivalence (BE) test, which essentially is a comparative clinical study of the generic versus the branded medicine, in healthy volunteers. This is a costly test and the question has come up if reliable and less expensive laboratory test(s), so-called *in vitro* BE tests, also are powerful to assess the 'appropriateness of the generic'. Such *in vitro* BE tests need to be responsive to physiological differences that would cause the generic to be different from the branded medicine. One of such physiological differences is a difference in gastrointestinal (GI) permeability, to which a validated *in vitro* BE test is not available yet.

The goal of BIOTHREE was to develop such a test, using *in vitro* permeability through a cell culture membrane as model for *in vivo* GI permeability. This new *in vitro* BE test should be validated by comparison with the *in vivo* BE test, using generics that are *not* good copies. In 2010, a model drug substance (acyclovir), a permeability modulator (chitosan) and the investigational dosage form (dispersible tablets) have been selected. Final results are not yet available.
A second part of this project is BIOWAIVER, a parallel research programme consisting of literature searches, in which for the most essential medicines the reliability of the yet available *in vitro* BE tests for that medicine are reviewed. The results were used in the revision of the European Medicines Agency (EMA) guideline on BE and were also used in the pre-qualification program of the World Health Organisation (WHO).

In the Netherlands the level of generic prescriptions has recently passed 60%. Therefore in depth knowledge, based – in part – on own experimental research, of issues related to the assessment of the appropriateness of generics is essential.

7 Theme Environmental quality and health (EQH)

7.1 EQH objectives

The EQH theme reflects the diversity of RIVM's Environment and Safety Division, to understand policy options, but other divisions are involved in assessing environmental health effects. Monitoring remains vital in many environmental areas, such as particulate matter. Risk assessments for encouraging healthy environmental conditions or evaluating economical activity are becoming increasingly important. More research needs to go into identifying behavioural scenarios and risk perceptions. Complicated risk assessments and environmental health impact assessments need to be developed.

Programmes
Research projects in this theme are grouped into four programmes:

- Risk assessment;
- Interface risk assessment and environmental health impact assessment
- Environmental health impact assessment;
- Measurement methods.

7.2 Summarised outcome of EQH

The 'Environmental quality and health' projects have led to an increased knowledge on the fields of risk assessment, environmental health impact assessment and measurement methods. Twenty two projects have been carried out. Four projects are still continuing in 2011 and beyond. The results of most projects are mentioned, even if they are not finished yet. Only one project that started in 2010 is not discussed, because it was just a preparatory study for a project that started in 2011. All project titles are mentioned in Appendix 1.

Risk assessment
Assessing a wide range of environmental risks is an important task in RIVM's core business. Existing risk assessment methods need to be updated permanently, and new methods are required to assess new risks. Because of the wide range of environmental risks, a wide range of assessment methods are needed. In this theme, RIVM has developed new methods and testing procedures, and improved existing methods. To assess the consequences of exposure to electromagnetic fields a set of new different measures, which improves the current measurements, has been developed. Standard procedures of risk assessment of fungal metabolites, necessary to assess biological control agents, are not available yet. Progress has been made in the development of such procedures. Furthermore, progress has been made in developing more efficient development toxicity testing, with the potential of using less experimental animals.

Risk assessment does not only apply to individual risk factors; usually a combination of risk factors occurs. Fundamental methods meant for a broad array of policy fields have been developed, for instance to be used in chronic impact protection or disaster management. Furthermore, on the development of methods to be used at the local level and integrated testing strategies, that aim to reduce animal testing, very good progress has been made.

Interesting results have been obtained on the assessment of climate and ozone change effects, related to the role of sunlight and UV-exposure on the causes of cancer.

Interface risk assessment and environmental health impact assessment
Modelling is an important instrument in estimating health effects of different risk. Although much is already known about the risks of ionising radiation, more knowledge is needed on low levels of radiation, because they are ubiquitous. By extrapolations more insight has been gained. To assess possible health effects related to medicines and chemicals, the applicability of a new approach, pharmacokinetic-pharmacodynamic modelling has been tested, with promising results.

Environmental health impact assessments
Environmental health problems are increasingly complex and uncertain. Impacts are embedded in a wide societal context. To assess and compare health impacts, news ways are urgently needed and current methods need improvement. To develop adequate methods, a wide variety of expertise is necessary. For this, close collaboration with other experts in the Netherlands and abroad has been set up. Together steps have been put forward into the development of adequate environmental health impact assessment methods, meant to support policymaking. Work was targeted on human health as well as ecosystems. A versatile assessment methodology and appraisal framework has been developed and tested on different stress factors. Also monetary factors have been considered.

Of course, uncertainties exist in all methods. To improve existing methods, new ways for uncertainty assessment have been developed. Results on air pollution have been implemented in RIVM's Chronic Disease Model.

More detailed information has been gained on the risks of particulate matter. The potential risk of particulate matter has been known for a long time, but scientific research indicates that the actual health risk depends on the specific characteristics of emission sources, so more knowledge on underlying mechanisms is needed. Different health effects appear to depend on size fraction, composition as well as oxidative potential. The results are to be incorporated in existing environmental health impact assessments.

It is important to know people's perceptions of risks, because they may differ from expert judgements. As this is essential to anticipate deliberations and risk communications, more knowledge has been acquired on layperson's concern of different risks. These observations give policymakers an opportunity to make proposed measures more tailor-made.

Measurement methods
Adequate environmental and health policy depends on appropriate information. RIVM invested in adequate measurement methods and instruments to be able to assess a wide range of parameters. An example is the development Leaching Assessment Device, a device to intercept the drainage flux from soil surface to the water saturated zone to the ground water.

Climate and air quality monitoring is especially relevant because climate changes will have important consequences for spatial planning and economy. RIVM has, through it strategic research, contributed to the national focal point

for collaboration on climate monitoring at Cabauw, which resulted in advanced techniques such as a new remote sensing instrument. This technique has also been used to collect information on the relationship between meteorological and atmospheric parameters, and the amount of night time light on the ground. This information is relevant to establish adverse affects of artificial light during the night. Furthermore, an operational system for air quality smog modelling and forecasting had been delivered.

Noise exposure might cause annoyance, resulting in disturbed sleep quality and adverse health effects. Nationwide maps of background noise from different sources are available now, as well as more knowledge on e.g. tonal aspects of noise from motorways and wind turbines. Also perception of noise has been taken into account, by performing a study in the Rotterdam-Rijnmond region. The latter is important because there appears to be a limited correlation between perceived annoyance and measured exposure.

7.3 EQH project results

In Appendix 2 an internetlink to the full list of publications is provided. The list will be updated on a regular basis. The project numbers are mentioned below and in the list of publications.

S601001 Dr. T.G. Vermeire ITS: integrated testing strategies
According to REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals), the European legislation on chemicals and their safe use, about 30.000 chemicals have to be assessed regarding their (eco-) toxicological effects. Current testing strategies ask for a large number of experimental animal data. However, REACH also aims to reduce animal testing where possible.

The aim of this project was to develop alternative strategies, so called Integrated Testing Strategies (ITS). The project is part of a European Framework Project OSIRIS (Optimised Strategies for the Risk Assessment of Chemicals). ITS are intended to decrease the use of animal testing, *in vitro* testing and non-testing information using a weight-of-evidence approach, backed by statistical decision analysis. ITS aims to shift risk assessment from an approach with extensive animal testing to a more efficient, context-specific and substance-tailored approach. In this way full advantage can be taken of existing information by grouping information about similar substances and integrating exposure considerations in the decision making. In this project, ITS have been proposed for the assessment of skin sensitisation, mutagenicity and carcinogenity, repeated dose toxicity, aquatic toxicity and bioconcentration. All these ITS are implemented in a web-based OSIRIS tool which will be made freely available for end-users ranging from industry to regulatory authorities and academia.

The OSIRIS Web tool will be offered to the European Chemicals Agency and will contribute to the reduction of the use of experimental animals for safety testing of chemicals.

S601150 Drs. E. Rorije Developmental toxicity analysis
Developmental toxicity testing of chemical substances is necessary for risk assessment of chemicals. However, testing for this property requires a relatively large number of experimental animals. Use of more efficient testing protocols and careful analysis of all existing developmental toxicity data make it possible

to reduce this number as indicated by our earlier retrospective analysis of all published developmental toxicity tests.

Therefore two separate issues with relevance to developmental toxicity for chemicals risk assessment have been investigated. First the sensitivity of all parameters currently measured in developmental toxicity testing, and secondly the relevance of different *in vitro* estrogen receptor assays test for screening or predicting developmental toxicity. A sensitivity analysis of the parameters used in the reproductive toxicity test needing two generations has lead to acceptance of a single generation test, potentially saving up to 1200 animals per test. The publication of the estrogen receptor analysis currently plays a role in international expert discussions in the Organisation for Economic Cooperation and Development (OECD) on simplification and harmonisation of testing for potential endocrine disruption of chemicals.

Our results have led to international recognition on the one hand and a potential reduction of the use of animal experiments on the other hand.

S601151 Dr. J.W.A. Scheepmaker Fungal: Risk assessment fungal metabolites
Entomopathogenic fungi (EPF) are being developed as biopesticides to control a range of arthropod pests. EPF have yielded several important bioactive metabolites including the anti-cancer compound swainsonine and the immunosuppressant compounds cyclosporine and myriocin. Many new compounds are being discovered each year and new properties are being attributed to known compounds. For the introduction of biological control agents (BCAs) on the market, a registration of the BCA including EPF and their 'relevant' metabolites is needed. In first instance an answer must be given on the question: what is a relevant metabolite? This is of crucial importance for reducing the amount of work that has to be done for the preparation of a registration dossier, which is in turn crucial for the success of the BCA.

This study gives a broad overview of the range and quantities of metabolites and their variation among strains. The metabolite profiles and quantities depend on culture conditions, extraction methods and detection methods. This information is necessary in setting criteria for determining the relevant metabolite.
The project will enhance the development of a standard procedure of risk assessment of the fungal metabolites in the EU. If the proposals are acknowledged by the Organisation for Economic Co-operation and Development (OECD), the risk assessment also will be harmonised worldwide.

S607001 Dr. L. Posthuma EIA: environmental impact assessment
Since risks of contamination for the environment are very frequently found, policy attention is needed to rank kinds and magnitudes of impacts in contaminated systems, for example in relation to ecosystem services to man. To strengthen policymakers in risk management of contaminated environments, RIVM has developed general methods to quantify environmental impacts on and hazards to sustainable use of stressed ecosystems. Environmental Impact Assessment (EIA) is a theoretically based and validated approach to handle current policy problems in risk assessment and management. Urgent issues are: 'How bad is bad when criteria are exceeded?', and 'What are sustainability impacts of multi-stressed ecosystems?'.

EIA has delivered fundamental methods to use in a broad array of policy fields, ranging from chronic impact protection and management to disaster management. Amongst others, the EIA project team developed the model FEAT

(Flash Environmental Assessment Tool), to be applied by UN-disaster teams upon (possible) release of massive amounts of dangerous chemicals after e.g. a tsunami or a landslide. FEAT is currently used by United Nations Disaster Assessment and Coordination as post-disaster impact reduction tool. In addition, FEAT is reshaped into HITs, local Hazard Identification Tools, implying that local authorities increase their disaster preparedness.

Despite the very narrow unifying theme (what happens to ecosystems exposed to multi-stress and what does that mean for sustainability of Ecosystem Services), the research area was very wide, and the project products addressed issues as variable as ‘mixture risk assessment’, ‘food-web stability’ and ‘disaster preparedness’. Likewise, the projects’ results are already widely used in a variety of policy fields.

S607002 Prof.dr. A.M. Breure RCIERA: research cooperation in ecological risk assessment
The Water Framework Directive makes integral assessment of effects on the total ecosystem of soil and water necessary (stress ecology). Ecosystem responses to changing environmental conditions must be known to predict the changes. To quantify the stress effect on the composition of communities of organisms in ecosystems, the indicators must focus on different organisational levels, e.g. a cellular, species, or community level. The effects of single stressors and of combinations of stressors are to be known because they may interact with each other and multiple stressor effects may be larger (synergism) or smaller (antagonism) than expected.

Ecotoxicogenetics (the research on the effects of toxicants on gene expression) is generally seen as a promising technique that would give insights in the mechanisms of the toxic effects.
Theoretically, effects of toxicants on gene expression could be present at lower concentrations than the concentrations that will affect whole organisms. This might provide an early warning signal by extrapolation of these insights to effects on whole cells or individuals. We had to conclude, however, that literature data do not support this view. This research line is replaced by developing techniques on the species level. The different approach is based on the relationships between the species diversity and abundance in ecosystems and the environmental quality. The relationship between the size of organisms and the abundance can be used as a measure for the extent to which an ecosystem is disturbed.

Based on this relationship we developed an indicator for the effects of single stressors and mixtures on ecosystem composition.

S630006 Drs. C.M.A.G. van Wiechen SMARAGHT: small area health analysis, a geographical toolkit
The public’s interest in the actual health consequences of environmental risk factors at the local level increases. If citizens notice unusual aggregations of a disease in a small neighbourhood they tend to attribute it to a nearby source of pollution. This public concern asks for an adequate and quick response. To investigate the claims, it is essential to have access to reliable disease incidence or prevalence data in a given area. Information on the number of observed cases as well as the number of expected cases from a comparable reference population must be available. Such information can be accessed through a ‘toolkit’ facilitating environmental health research with routine health data in small geographic areas.

The developed toolkit contains tools for disease mapping, risk analysis, and disease cluster analysis. Access to data on exposure and on population and confounders is part of it, as is expertise on the decision making pathway for using the toolkit. The tools were applied to a case study in which public concern was raised about a supposed positive relation between air pollution from a large steel plant in the Netherlands and lung cancer in a village near the plant.

In conclusion, the present toolkit did contribute positively to the environmental health discussions in society and improved communications with policymakers, the local community, and other parties involved.

S610002 Dr. H. Slaper COURSE: climate and ozone change effects
Climate and ozone changes can have important implications for the solar ultraviolet (UV) radiation received at the ground. Solar UV radiation has effects on human health, air quality, aquatic and terrestrial ecosystems and food chains. UV exposure has a strong causal relation with skin cancer and cataract. Low UV exposure can lead to a deficiency in vitamin D production in the skin. RIVM now has a unique 17 year continuous data record on the UV radiation levels in the Netherlands. The data is provided live on www.rivm.nl/zonkracht and is used in the ozone assessment reports from the World Meteorological Organisation (WMO). RIVM analysed UV radiation levels combining UV measurements with UV reconstruction techniques. It was shown that the upward changes in UV radiation levels in Europe were partly due to ozone depletion, but also partly due to cloud changes. This illustrates that future UV radiation levels are also directly influenced by climate change. Predictions on future developments in the cloud reduction of UV remain uncertain.

Using RIVM's Assessment Model for Ultraviolet radiation and Risks (AMOUR) a 5-10% future increase in skin cancer incidence in the Netherlands is calculated as a consequence of observed ozone depletion and expected future recovery. The AMOUR model is now suited for global calculations, and includes a differentiation in skin sensitivity of the global population and a preliminary cataract incidence module. The global analysis uses satellite data to retrieve spatial variability in UV radiation levels at the ground and the trends therein. RIVM performed validation studies for these retrieval techniques. Furthermore, RIVM participated in a working group of the Dutch Cancer Society on the relation between cancer, sunlight and vitamin D and contributed a chapter to the final report.

S610001 Dr H. Bijwaard MIRACLE: modelling ionising radiation and cancer for low dose effects
Low levels of ionising radiation are ubiquitous. Everyone is exposed to it from the cosmos, medical examinations, nuclear waste, body scanners, and sources of radon and possibly from nuclear accidents. Extrapolations from A-bomb effects (based on high levels of radiation) predict some 2000 cancer deaths from radiation in the Netherlands per year. These rather simple extrapolations call for better risk estimates of the lower end of the dose-response relationships for several types of ionising radiation exposures and cancers.

Three types of cancer: leukaemia, lung cancer and breast cancer have been modelled. For leukaemia this resulted in information that contributed to a better understanding of leukaemia incidence near nuclear power plants. For lung cancer the synergetic effects of both radon and tobacco to lung tumour development were reported. For breast cancer radiation risks turned out to be

considerably lower than estimated previously. Thus breast cancer screening might be started earlier and perhaps also be performed more frequently.

The research conducted in this project has contributed to a better understanding of the low dose risks for leukaemia, lung cancer and breast cancer, three cancers that are frequently induced by ionising radiation. Apart from the dose dependence effects, this project obtained new insights into the dependence of risks on dose rate, age at exposure and radiation quality.

S660150 Dr. C.C. Hunault PKPD modelling in human toxicology
The National Dutch Poisons Information Centre (NVIC) is responsible for providing advice to health professionals and rescue teams on a 24/7 basis, both for individual cases and major public health threats. Advice covers the possible health effects related to medicines and chemicals and the corresponding adequate therapies. The use of a new approach, PK/PD modelling, might be of help in clinical toxicology to provide more accurate and complete advice.

Pharmacokinetics (PK) is the process by which a drug is absorbed, distributed, metabolised, and eliminated by the body. Pharmacodynamics (PD) is the study of the action or effects of drugs on living organisms. PK/PD models are mathematical models that can estimate time-course concentrations of drugs and compounds for different exposure conditions. PK/PD modelling also helps to better evaluate the interactions between different medicines or chemicals and the difference in susceptibility to medicines or chemicals between different members of a human population. PK/PD modelling thus provides useful results for forensic toxicology.

This project has given more practical insight in PK/PD modelling. The kinetic cannabis model RIVM that has been developed, to follow concentration and time-course of the active ingredient THC after smoking cannabis cigarettes, containing high doses of THC mixed with tobacco, might serve as an example. This model can estimate the time of cannabis exposure based upon individual THC serum concentrations. Taking a blood sample at a particular time point, it is now possible to evaluate from this point what the actual concentrations might have been in the time period before the sample has been taken.

S610150 Dr. J.F.B. Bolte KINESE: Validation of key exposure indicators in epidemiological studies on electromagnetic fields
Potential consequences of exposure to electromagnetic fields (EMF) are a contemporary issue. EMF exposure is related to a range of communication transmitters, e.g. FM radio, TV, mobile phones and base stations for mobile telecommunication, Digital Enhanced Cordless Telecommunication phones and wireless internet. To be able to answer future questions about the association between actual exposure to EMF and adverse, non specific health effects, the current measurement methods, both for exposure and outcomes, need to be further developed, validated and harmonised.

To get a better insight in the exposure, personal exposure measurements and questionnaire data gathered in a running study, related to demographics, housing parameters, time-activity patterns and use of mobile phones and electric equipment were used for secondary analysis. Based on personal exposure measurements during daily activities, a set of different measures could be calculated. This set aimed to characterise the features of the 24 hours exposure to the electric fields. Comparison of different exposure measures with the questionnaire data only resulted in weak correlations. Also the first results

on the association between the medically unexplained physical symptoms and personal exposure measurements over 24-hours were weak. However, we were able to point out the most important demographic features to predict the personal exposure.

The result of this project is a new questionnaire with key questions for estimating exposure to electromagnetic fields. This is currently used in a new project supported by ZonMW (Netherlands organisation for health research and development).

S630001 Prof.dr E. Lebret IRAS envionmental health collaboration
Environmental health impact assessment is a core activity of RIVM in order to advice the government on complex environmental health issues. To increase expertise a strategic cooperation with the Institute of Risk Assessment Sciences (IRAS, University of Utrecht) was strengthened.

The cooperation has developed along two lines: research to characterise traffic-related exposures and health effects as one line. This work used hybrid epidemiological-toxicological methods. Results indicate source and location dependent health effects of particulate matter, both *in vitro* and *in vivo* (animals and human volunteers). The results can be used for future revisions of the standards for fine particulate matter and for policy development.

In the second line, impact indicators from different domains have been developed and applied in integrated environmental health impact assessment. These include environmental disease burden estimates such as environmental DALY (Disability Adjusted Life Years) and monetisation of societal cost associated with environmental health problems. Results showed a somewhat higher willingness-to-pay (WTP) to avoid effects from air pollution as compared to noise effects, with substantial differences within and between 5 participating countries. Policymakers increasingly seek to financially compensate affected people, instead of (the more costly) reduction of environmental exposures. However, willingness-to-accept (WTA) financial compensation for environmental health risk has hardly been studied. This study shows that WTA amounts were about 15 times higher for the same environmental health effects than WTP, again with substantial differences within and between countries.

This collaboration has – apart from the findings described above – resulted in a strong strategic alliance and was even broadened to electromagnetic fields in relation to medically unexplained symptoms.

S630002 Dr. N. Janssen RAPTES: risks of airborne particles
Exposure to ambient particulate matter (PM) air pollution is associated with several health effects, including reduced life expectancy and increased respiratory and cardiovascular disease.
The aim of the project was to characterise the physical, chemical and oxidant properties of inhaled PM and establish which of these characteristics are critical determinates of adverse systemic and respiratory effects seen after PM exposures.

In summary, it was possible to successfully identify and characterise real-world situations with very different particle characteristics. High contrast and low correlations between PM characteristics, as well as consistency of these differences, provided a basis for identifying health relevant PM characteristics in

further studies. These included *in vitro*, *in vivo* as well as human volunteer studies.

In these studies it became clear that size fraction, PM composition as well as oxidative potential contribute to PM induced health effects, and that the critical determinants of PM differ for different health effects.

S630003 Dr. A.B. Knol VAMPHIRE: versatile assessment methodology project for health impacts and the risks in the environment
Environmental health problems are increasingly complex. Therefore, in line with the policy framework Dealing Sensibly with Risk, modern day impact assessments are more inclusive than traditional risk assessments. To evaluate the multifaceted aspects of the complex environmental health impacts and risks, a versatile assessment methodology and appraisal framework has been developed.

A core set indicators for complex environmental health problems comprises policy (performance) indicators, environmental burden of disease (eBoD) indicators, monetary aspects of the health impact and risk perception and acceptance. This framework was introduced, further developed and applied in the EU project INTARESE (Integrated Project of Health Risk of Environmental Stressors in Europe). The eBoD methodology was advanced to include life table approaches and showed that the Netherlands have relatively low eBoD for radon, dioxin, ozone and benzene and relatively high eBoD for traffic noise. Expert elicitation procedures were developed and applied for ultra fine particles (UFP). This now allows tentative inclusion of UFP in impact assessments. Questionnaires on willingness-to-pay and on risk perception were applied in a multi-country setting. A case study on transport policy measures in The Hague showed that the monetary value of the total health benefits from the traffic circulation plan was projected to be about two million euros up to 2020. Two thirds would be health benefits from noise reduction, one third due to cleaner air. Environmental equity effects were also observed in this case study.

In summary this project resulted in new tools to evaluate complex environmental issues is a practical way.

S630004 Dr. A.B. Knol IQARUS: uncertainty in environmental biological oxygen demand
Environmental health problems are becoming more and more complex and uncertain factor play an increasingly important role. Risks like climate change or obesity have many different causes and impacts and are embedded in a wide societal context. Because these risks are challenging to comprehend, science is finding new ways to assess such risks in a policy-relevant way. In order to compare the health impacts of different environmental problems or to prioritise policy alternatives, environmental health impacts may often need to be compared. Aggregated indicators, such as the ‘burden of disease’ which expresses divergent health impacts in one number, make diverging environmental health problems comparable. However, the many uncertainties are often difficult to deal with in a comprehensive and meaningful way.

This project aimed to identify, quantify and reduce uncertainties in environmental health impact estimates. Amongst others, the project delivered new methods for uncertainty assessment and for organising expert elicitations within the context of assessing complex environmental health risks. The methods developed in IQARUS contributed to the wider development of methods

for integrated environmental health impact assessment. In addition, an expert elicitation on the causes and health effects of exposure to ultra fine particles, the smallest components of particulate matter air pollution, extended the necessary knowledge on the subject.

The project thus enabled RIVM to support decision makers better and allows policy preparation for diverging issues that need an integrated answer.

S630005 Dr. R. van Poll PACEHR perception, appraisal and communication of environmental risks
The Appraisal Framework Health and Environment (AF) is a tool to describe the scientific evidence on environmental health problems.
The AF addresses five issues of environmental health problems:

- extent of the health effects;
- severity of the health effects;
- perception of the risk;
- possibility of interventions; and
- cost and benefits.

Some of the issues were treated rather qualitatively in the AF, in particular the psychometric aspects (e.g.: dread, controllability, reversibility, voluntarism) that determine risk perception. There is, however, little information on consistency and intra-individual variation in risk perception when applied to specific risk problems. The main question of this project was how to describe these aspects more quantitatively when evaluating risk problems. In six European countries residents' risk perceptions on nine different risks were assessed: e.g., air pollution, sea level rise, corrosive cleaning agents, tanning, dampness, polluted tap water, nuclear waste, alcohol consumption, and pesticides in food.

In general people appear to be most concerned about the health risks of 'air pollution due to traffic' and 'pesticides in food'. Concern is lowest about the health risks of alcohol consumption. The difference in extent of concern about the risks is reflected in the differences in scores on the risk aspects. The relevance of these findings is that they indicate which risks are the most worrisome among the general public and cause the most concern and for what reasons. For air pollution the reasons are: the risk is dreaded, surrounded with lack of knowledge and information, affecting a lot of people, it is considered involuntary and with unbalanced (dis)advantages. This latter observation gives policymakers an opportunity to make policy more tailor-made.

S680001 Dr.ir. W.A.J. van Pull NITROGEN: relating groundwater and air quality for nitrogen
The presence of excess of nitrogen causes severe environmental problems like eutrophication of nature areas, a loss in biodiversity and pollution of drinking water. The burden to the environment has been decreased in the last decennia but will remain a rather persistent problem for the next future.
This project has resulted in improved nitrogen deposition estimates on natural areas by taking into account the characteristics (structure, vegetation type) of the area. The improved deposition estimates are used in the current assessment of the effects of nitrogen deposition on Natura2000 sites. Methods have been developed and tested with which the deposition of ammonia can be measured in nature areas.

The existing SMARTml model has been extended by a vegetation module and can now be used to calculate present nitrogen leaching in nature areas

nationwide as a function of the atmospheric deposition of nitrogen. With the model now it will be possible to explain the relationship between nitrogen depositions and leaching in nature areas, and the observed levels and trends therein. Moreover with the SMARTml model an analysis of the nitrate leaching on a national scale can be obtained, also under nature areas where no measurements are available. Also the effects of policy measures on nitrogen emissions and effects of climate change can be evaluated now.

S680002 Dr. A. Apituley CESAR: climate and air quality monitoring
The Cabauw Experimental Site for Atmospheric Research (CESAR) is the national focal point for collaboration on climate monitoring and atmospheric research. It has unique possibilities for validating and improving satellite measurements of aerosols and particulate matter. CESAR combines many essential measurements that are needed to reduce uncertainties in our understanding of the climate. The CESAR site plays the role of an advanced observatory for climate and air quality monitoring. This is important because air pollution can affect climate change through feedbacks in cloud processes. Moreover, climate changes, causing sea level rise and change of precipitation patterns, will have important consequences for spatial planning and economy. And finally airborne particulate matter (PM) and aerosols can also lead to a wide range of detrimental health effects.

RIVM contributes to CESAR and has added advanced techniques to a remote sensing instrument installed at CESAR for temperature measurements. This instrument was able to provide a unique dataset for determination of volcanic ash particles during the eruption of the Eyafjallajoküll in Iceland in 2010. Since aviation authorities needed to respond rapidly to the situation, there was a high demand for near real-time data. In collaboration with KNMI, novel retrieval methods developed in this project could be successfully applied. Active collaboration took place at national and international level, in particular through the European Aerosol Research Lidar Network (EARLINET).

SOR investments have given RIVM a reputation and strategic place in an alliance important for climate and health research.

S680003 Drs. D.P.J. Swart AQURES: Air quality and remote sensing
The measurement of air quality over Europe largely depends on a patchwork of ground based national and regional monitoring networks. AQURES has integrated this existing infrastructure, combined it with air quality measurements from satellites, and assimilated all these observations in a chemical transport model.

The result of this project is ‘SmogProg’: a system that provides a very detailed picture of the air quality over Europe as it changes from day to day and from hour to hour. It also produces a more accurate and more detailed air quality forecast. As satellite observations were used in this way for the first time, AQURES included a large international campaign that checked the quality of these measurements. Important for environmental policy is SmogProg’s capability to make annual assessments and to determine trends. For public health SmogProg provides local health authorities and individual citizens with an air quality forecast that is specific in time and place. This is especially relevant during smog episodes and of special interest to people with respiratory diseases.

Since June 2009, SmogProg is used on a day-to-day basis by the RIVM to provide the Dutch air quality forecast. This forecast is available on the web (http://www.lml.rivm.nl/verw.html).

SmogProg was developed as a joint effort by RIVM, the Netherlands Organisation for Applied Scientific Research (TNO) and the Royal Netherlands Meteorological Institute (KNMI) in a project lead by RIVM. SmogProg results are also contributed to European air quality projects.

S680004 Ir. J. Jabben NOISE: improving noise exposure assessments
Enduring high environmental noise exposure can cause annoyance and result in disturbed sleep quality and health effects, such as high blood pressure and cardiovascular effects. Noise exposure is usually rated by a single indicator for the yearly average noise level. As tonal and dynamical noise aspects are disregarded, this indicator is often a poor predictor of effects. The project aimed at establishing a more complete picture of noise exposure in the Netherlands, in which tonal character and dynamic behaviour of noise levels over time are considered.

The project resulted in nationwide maps for background noise from roadway, railway and airport noise. Also tonal aspects of noise from motorways and wind turbines and noise sensitive areas for airport noise were investigated. The results do not offer a complete noise picture yet, but do provide important additional information for policymakers. Noise measures merely taken at locations of high average exposure do not fully indicate problems on a larger scale, while background noise levels continue to increase due to ongoing mobility growth, particularly for road- and airport traffic. Along motorways with much heavy freight traffic, tonal character may lead to less effective reduction by sound barriers and result in increased annoyance.

The results concerning the inventory of wind turbine noise are important for assessing the impact of new wind turbine parks. The sensitivity maps of urban areas for airport noise are now at use by the Dutch air traffic control, for quieter design of airport departure routes.

S680150 Ir. J. Jabben Noise and health in the Rijnmond
This study of the relationship between noise and its health effects in the Rotterdam-Rijnmond region was an investigation of new noise indicators and their relation with perception. Conventional noise policies in the Netherlands are costly and focus on reducing or avoiding high noise levels at the façade of individual dwellings, although their correlation with perceived environmental quality is limited. The project goal was to find out if the overall perceived noise quality within a specific area can be related to more generalised noise indicators, which rate the total noise exposure of its population as a whole.

To this aim, group noise levels were determined for postal areas in the Rotterdam-Rijnmond region for average exposure, peak exposure and for low frequency noise. The project showed that in areas with high group levels caused by wind turbines or industry, more often complaints of low frequency noise occurred. High group noise levels for peak noise could be related to increased complaints due to high speed train passages. In a next study the group approach will be refined and more perception data will be gathered.

The ‘group noise level’ is a useful concept in formulating effective noise policies. For example it can be used for rating and comparing the noise impact of different airports. Prioritising noise measures based on group noise levels will be cost effective, as measures will only apply in case a sufficient amount of dwellings is exposed.

S680151 Dr. D.E. Lolkema Brightness of the night sky
Artificial lighting at night, needed in populated areas, has adverse effects on flora and fauna as well as on humans. Recently, policymakers, nationally and locally, have become more interested in the impact of artificial lighting at night. This impact however, can not be known without knowledge about the exposure of flora, fauna and humans to artificial light. This exposure, quantified by the night sky brightness, depends on the surrounding light sources in combination with atmospherical conditions. For example, the sky close to a strong light source, like a greenhouse, a large city or an industrial area, can be quite dark on clear nights, i.e. without clouds or an optically thick aerosol layer. But on cloudy nights this same sky can be very bright due to light scattering by these same clouds. So the emission being the same, the exposure can largely differ.

To assess the effect of atmospheric conditions on the night sky brightness, measurements have been performed with three different light meters at the Cabauw Experimental Site for Atmospheric Research (CESAR) for a period of almost one year. At this site a wealth of atmospheric properties is monitored. This pilot study revealed a clear correlation between night sky brightness on the one hand and cloud cover and cloud base height on the other. A correlation between night sky brightness and particulate matter mass concentration could not be established.

The results of this study give us insight in the variability of night sky brightness and are of value to model calculations of night sky brightness based on light emission data.

Appendix 1 Themes, programmes and projects 2007-2010

A full list of projects, started between 2007 and 2010, is given below. Only the projects with results worth mentioning are described in this report. Some of the project have only recently started.

* Project continues after 2010

Theme RPC

Programme	Projectnr	Project leader	Title	Start	End
Experimental (animal) studies in risk assessment	230136	Ing. J.H.J. Reimerink	Proteomics for population screening	2007	2010
	320001	Dr. P.M.J. Bos	Population based biokinetic modelling	2009	*
	320002	Prof. dr. F.X.R. van Leeuwen	Improvement of risk assessment	2010	*
	340001	Dr. A. de Vries	Adverse effects of circadion disruption	2010	*
	340010	Dr. M. Luijten	Toxicogenomics in risk assessment	2007	2009
	350010	Dr. Ir. M. C. Ocké	Methods for dietary exposure assessment	2007	2010
	340050	Dr. L.T.M. van de Ven	Alternatives for animal testing	2007	2010
	340030	Dr. W. H de Jong	Nanotechnology, potential risks	2007	*
Information to consumers	270126	Drs. H.C. Ossenbaard	gettingBetter.nl	2007	*
	260196	Prof.dr. G.P. Westert	Effective use performance indicators	2007	*

Theme ERF

Programme	Projectnr	Project leader	Title	Start	End
Measuring and modelling	330006	Dr. B.J. van Rotterdam	Biothreat DNA micro-arrays	2007	2010
	620001	Dr. P.A.M. Uijt de Haag	QRA: quantitative risk assessment	2007	*
	630007	Drs. F.S.M. Stom	Rapid assessments after disasters	2007	2010
	609001	Dr. S.M. Hoffer	Terrorist attacks	2007	2008
Risk assessment in emergencies	610003	Dr. C.J.W. Twenhöfel	ERFRAD: Emergency response function for radiation	2007	2010
	609002	Drs. Ing. N.J.C. van Belle	From sub acute to acute response	2007	2010
	609150	Dr. Ir. L. Grievink	Health 10 years post-disaster in Enschede	2010	2010
Clinical toxicology	660001	Prof. Dr. J. Meulenbelt	Research cooperation in human toxicology	2007	*

Theme INF

Programme	Projectnr	Project leader	Title	Start	End
Modelling	210026	Dr. H. Grundmann	Modelling the future of MRSA in NL	2007	*
	210036	Dr. J. Wallinga	Tracking emerging epidemics	2007	2010
	210046	Dr. J. Wallinga	Epidemic modelling of molecular data	2007	2009
	210056	Dr. M. E.E. Kretzschmar	Chlamydia positivity and prevalence	2008	2010
	210066	Dr. J. Wallinga	Who infected whom	2009	*
	210076	Dr. M. E.E. Kretzschmar	Timeliness response during outbreaks	2009	*
Immunology	230426	Dr. A.M. Buisman	Memory immunity	2007	*
	230146	Dr. B. Pinelli[1] Ortiz	Immunomodulation by helminth molecules	2007	-
	230166	Dr. B. Pinelli Ortiz	Zoonotic helminth infections and allergy	2008	*
	230406	Dr. C.M. Janssen	Host-response to RSV (Respiratory Syncytial Virus)	2007	*
	230416	Dr. R.S. Van Binnendijk	Immune pathways in vaccination	2007	2010
	340002	Dr. C.M. Janssen	Effect of paracetamol on vaccination	2010	*
Genomics	230136	Dr. D. v. Soolingen	Whole genome analysis of M. tuberculosis	2007	*
	230436	Dr. A.J. King	Microarrays to map pertussis adaptation	2007	2010
	230446	Dr. F.R. Mooi	B. pertussis adaptation to vaccination	2007	*
	330116	Dr. H. Sprong	Ticks: Trojan horses with new surprises	2008	*
INF - other	210086	Dr. H.E. de Melker	Set-up monitoring acceptance NIP	2010	*
	230156	Dr. E. Duizer	Transmission intervention strategies	2008	*
	V/330274	Dr. A. M. Roda Husman	VITAL: foodborn viruses	2008	2008

Speerpunt CIL

Programme	Projectnr	Project leader	Title	Start	End
Modelling chronic diseases	260146	Dr. Ir. W.M.M. Verschuren	Primary prevention research on cardiovascular diseases and diabetes	2007	*
	210116	Prof. dr. H.C. Boshuizen	Adaptable chronic diseases modelling	2007	2010
	260166	Dr. P.C.A. Droomers	Modelling SES disparities in health	2007	*
	350040	Dr.ir. J. Hoekstra	Modelling health effects of nutrition	2007	2009
Healthy ageing	206156	Dr.Ir. W.J.E.	Healthy ageing:	2007	*

[1] As of 2009, projects 230146 and 230166 have been combined

Programme	Projectnr	Project leader	Title	Start	End
		Bemelmans	overweight/underweight		
	340020	Dr. M.E.T. Dollé	Healthy ageing: gene-diet interactions	2007	*
Quality of care	260116	Prof. Dr. G.P. Westert	Health system performance	2007	2010
	270116	Dr. C.H. van Gool	Are diseases becoming less disabling?	2007	2010
	270166	Dr.J.Polder	Healthy ageing and health care expenditure	2009	*
	270156	Dr. J.S. de Koning	Hospital performance measurement	2007	2008
Economic evaluations	260176	Dr. T.L. Feenstra	Communicating uncertainty in economic evaluations	2008	
	260186	Drs. G. A. de Wit	Future unrelated medical costs	2007	2008
Other	350020	Dr. H.B. Bueno de Mesquita	Primary prevention research on obesity, cancer and ageing	2007	2010
	270126	Dr. A.J. Schuit	Knowledge transfer in public health	2007	*
	260126	Dr. A.H. Wijga	Lifestyle from childhood to adolescence	2007	*
	260136	Dr. A.H. Wijga	Chronic health problems in childhood	2008	2010
	270146	Dr.Ir. F. H.G.M. Hoeymans	Validation of data from general practise registries	2007	2008

Speerpunt MFF

Programme	Projectnr	Project leader	Title	Start	End
Not applicable	340001	Dr. F. Vroom	NOCEBO: negative perception to treatment	2010	2010
	340040	Dr. Ir. R.J. Vandebriel	Chronic drug use and autoimmunity	2007	*
	350030	Dr. Ing. H.J. v. Kranen	The food pharma interface	2007	*
	360001	Dr.Ing. A.M. Akkermans	Novel *in vitro* for pertussis toxin	2009	*
	360003	Dr. J.W. van der Laan	Carcinogenity of growth factors	2010	*
	360010	Dr. S.W.J. Janssen	Pharmaco-economical evaluations	2007	*
	360020	Dr. M.H.N. Hoefnagel	Immunogenicity of protein pharmaceuticals	2007	2009
	370010	Dr. D.M. Barends	Riskred	2007	2009
	370020	Drs. D. A. van Riet-Nales	MAGIC: Manipulation and administration of medicines given to children	2007	*
	370030	Dr. D.M. Barends	BIOTHREE	2008	2010

Speerpunt EQH

Programme	Projectnr	Project leader	Title	Start	End
Risk assessment	601001	Dr. T.G.Vermeire	ITS: integrated testing strategies	2007	2010
	601150	Drs. E. Rorije	Developmental toxicity analysis	2010	2010
	601151	Dr. J.W.A. Scheepmaker	Fungal: Risk assessment fungal metabolites	2010	2010
	607001	Dr. L. Posthuma	EIA: environmental impact assessment	2007	2010
	607002	Prof. Dr. A.M. Breure	RICIERA: research cooperation in ecological risk assessment	2007	*
	630006	Drs. C.M.A.G. van Wiechen	SMARAGHT: small area health analyses, a geographic toolkit	2007	2010
	610002	Dr. H. Slaper	COURSE: climate and ozone change effects	2007	2010
Interface risk assessment and EHIA	610001	Dr. H. Bijwaard	MIRACLE: modelling ionising radiation and cancer for low dose effects	2007	2010
	660150	Dr. CC. Hunault	PK/PD Modelling in human toxicology	2010	2010
Environmental health impact assessment	607150	Dr. L. Posthuma	ICQSAF: integrated contours of a quantitative sustainability assessment framework	2010	2010
	610150	Dr. J.F.B. Bolte	KINESE: validation of key exposure indicators in epidemiological studies on electromagnectic fields	2010	2010
	630001	Prof. Dr. Ir. E. Lebret	IRAS: environmental health collaboration	2007	*
	630002	Dr. N. Janssen	RAPTES: risks of airborne particles	2007	2010
	630003	Dr. A.B. Knol	VAMPHIRE: versatile assessment methodology project for health impacts and risks in the environment	2007	2010
	630004	Dr. A. B. Knol	IQARUS: uncertainty in environmental biological oxygen demand	2007	2009
	630005	Dr. R. van Poll	PACEHR: perception, appraisal and communication of environmental risks	2007	2009
Measurement methods	680001	Dr. Ir. W.A.J. van Pul	NITROGEN: Relating groundwater + air quality for N	2007	*
	680002	Dr. A. Apituley	CESAR: climate and air quality monitoring	2007	*
	680003	Drs. D.P.J. Swart	AQURES: air quality and remote sensing	2007	2010
	680004	Ir. J. Jabben	NOISE: improving noise exposure assessments	2007	2008
	680150	Ir. J. Jabben	Noise and health in the Rijnmond	2010	2010
	680151	Dr. D.E. Lolkema	Brightness of the night sky	2010	2010

Appendix 2 References 2007-2010

By the end of 2010, 353 scientific papers in peer reviewed magazines had been published of accepted. A full list of references is available on the internet (www.rivm.nl/SOR) and will be updated after 2011.

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