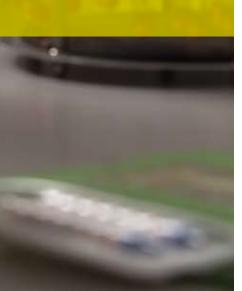


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National Institute for **Public Health** and the Environment



# Annual Science Report

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2005

# Annual Science Report

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**RIVM Annual Science Report 2005** 

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10 Will baby boomers stay healthy longer than their parents?

Just a few chemicals are causing most of the problems

Research papers, Books, Chapters & Reports, Doctoral Theses and Professorial Chairs

Nutrition, Medicines and Consumer Safety (RIVM-VGC)



Marc Sprenger, Director-General, National Institute for Public Health and the Environment (RIVM)

# **RIVM:** a research organisation at heart

In 1992, I was a young scientist wondering whether to apply for a job at the National Institute for Public Health and the Environment (RIVM).

At the time, I mostly thought of RIVM as an institute that produced solid policy reports - always reliable, sometimes a bit dense, and, it seemed, not often straight from the front lines of science. I confess that I had some doubts about whether such an institute really was the right place for me.

That changed, however, when I found out that Daan Kromhout, a nutritional epidemiologist at RIVM, had published exciting research papers in well-respected international research journals like The Lancet and the American Journal of Epidemiology. It made me realise that RIVM was a place where I would feel right at home; a policy-oriented institute where at the same time scientists carried out high-quality research.

The experience illustrates the importance of showing the world that, besides producing fine and increasingly accessible reports for governments at home and abroad, we also do a lot of excellent research. That message is at the heart of this Annual Science Report.

# Workable solutions

RIVM is a public institute. Society, most notably the Dutch national government, is its main client. Our mission is to translate our knowledge and expertise into workable solutions for problems our society faces today in the areas of health, nutrition, and environmental protection.

We counsel politicians and other policy makers on how to deal with the threat of emerging infectious diseases like SARS and pandemic flu; we explore how our country can enable its healthcare system to meet the demands of an ageing population and improve public health through prevention; we try to reliably assess the risks to our natural environment, whether it's from chemicals or radiation.

Another part of our work is to disseminate that same expertise to the public at large, using familiar as well as brand new means of communication. For example, we devise practical, Internet-based information tools such as 'Kies Beter', a state-of-the-art website that helps Dutch citizens make better-informed decisions on their personal health and healthcare. We will continue to find similarly innovative ways to promote our insights on health, nutrition and the environment to the rest of the world.

But at the same time people should know that RIVM at its core remains a scientific institute. Our researchers work closely with colleagues across Europe and the rest of the globe. Everything we do meets rigorous scientific standards and our research, which covers the gamut from radiation and toxicology to influenza and obesity, is published in international, peer-reviewed journals.

For our own RIVM staff too, this report has a lot to offer. I hope all our scientists will take the opportunity to re-acquaint themselves with the breadth and depth of our common research effort. All too often, we are so focused on finishing our own projects that we forget to find out what colleagues just down the hall have been up to. What's more, given our research areas and the fact that we are mostly funded by tax-payers, it's only fair that society gets the chance to learn about our research.

I hope RIVM researchers will also take home the message that rigorous science will always have a place at RIVM and that publishing top-notch papers in peer-reviewed journals is very important to us. In fact, I think we should celebrate such successes more frequently.

# Accomplishments

This Annual Science Report reinstates an old tradition at our institute. It demonstrates RIVM's scientific accomplishments by listing all research papers, books, book chapters, reports and doctoral theses our scientists published in 2005. It highlights a few of those publications, not because they're the best, but because together they represent the breadth of our multidisciplinary research. The report also gives some of our scientists a place in the spotlight; it tells us who they are, what they have done and what makes them tick. Like them, we should all explain to others what we are working on more often. For young researchers who may wonder about our identity, just as I did many years ago: This report should convince you that RIVM is, and will remain, a research organisation at heart. I hope that it's the kind of institute you, too, would like to join.

Marc J.W. Sprenger, Ph.D. MD

September 2006, Bilthoven, The Netherlands.

Director-General, National Institute for Public Health and the Environment (RIVM),

# Finding the Eschers in epidemic theories



Jacco Wallinga, Centre for Infectious Disease Control (RIVM-Clb) After the sudden appearance of SARS, the use of models to understand and beat outbreaks of infectious diseases gained importance. RIVM's modellers, too, have taken centre stage.

Jacco Wallings is a biologist first and foremost – but one not repelled by mathematical formulas. He likes to interpret rows of numbers that at first glance seem rather chaotic to find the systematic patterns hidden underneath.

As a pre-graduate at Wageningen University, Wallinga modelled the spread of rabies among foxes. At RIVM, he focuses on human infectious diseases like measles and pandemic flu. After the 2003 outbreak of Severe Acute Respiratory Syndrome (SARS), he sat at the table at the World Health Organisation (WHO) to assess the new virus's potential threat.

"Looking at these series of spikes representing the outbursts of new disease cases, I can't help but wonder: what's going on underneath?" Wallinga says. "What can we do to stop this from spreading?"

Statistical analysis, computer models and mathematical equations play leading roles in Wallinga's work. "Yet I get most excited about the biology, not the equations," he says.

# Escher drawings

The use of computers and mathematical models in biology often generates misunderstandings, Wallinga says. "Frequently people will ask me: 'We don't have any data, could you provide us with a model?' But without data, I have to tell them, there's nothing to model."

Another frequent misconception is that models are either 'right' or 'wrong', Wallinga says. "A model is a tool one uses to check the validity of a theory about biological mechanisms. When you try to translate your hypothesis into mathematical equations, inconsistencies will jump out pretty soon. It is like comparing epidemic theory with the famous drawings of M.C. Escher; while pieces of your theory can be accurate, the full picture may still be impossible. A mathematical model will quickly bring these errors to light."

In 2003, when the new, deadly SARS virus started to spread, Wallinga was working on an algorithm to convert timelines of flu cases into epidemiological models. He decided to enter the data on SARS cases that WHO put out on its website.

"The outcome shocked us," Wallinga says. "While WHO was reassuring people by saying SARS wasn't flu, our model predicted that it was actually worse. Harsh measures would be needed to contain the outbreak. We e-mailed our findings to a British colleague who was stationed at WHO during the SARS outbreak. It soon became clear that our predictions had been pretty accurate."

In May, when the outbreaks subsided, Wallinga was invited to speak at a WHO conference in Geneva. There he discovered other researchers had beaten him by submitting similar findings to Science, one of the world's premier research journals. Yet people in the modelling field knew RIVM was up to something. Speaking invitations kept popping up in his mailbox – in 2005 Wallinga addressed conferences in, for instance, Palm Springs (US) and Singapore. "The

More recently, Wallinga and his colleag a new flu pandemic. This time, while oth virus to spread like wildfire, with every p early with less dire predictions. Based or infections from every patient. Again, Wa other researchers had beaten them to th "but colleagues know who were among European collaborations." Sometimes, the team is more lucky. In 20 paper in PLoS Medicine (see sidebar). "W it's nice to see medical journals getting p now, although it's still a gamble. In the e real kick comes from suddenly spotting circus in which you have to play along." "At the moment, we're doing well. In 20 It's like the start of an epidemic. Let's ho do."

# Vaccination threshold sets the stage for major outbreak

Measles is a highly infectious, occasionally deadly viral disease for which a vaccine has been available for decades. In The Netherlands, over 90 percent of the population is vaccinated. Small subgroups don't, however, for mostly religious reasons. Unvaccinated members are susceptible to imported outbreaks unless they have been in contact with the virus before. Within these subgroups, susceptibility increases with time after the last major outbreak. Researchers checked Dutch vaccination records between 1976 and 2004 and related these to past outbreaks of measles. They discovered a threshold in susceptibility below which chances of a major outbreak are slim. When more than about 4.3 percent of the population becomes susceptible, however, the risk increases sharply. Further analysing the data, the authors estimated the benefit of vaccinating each additional child. When susceptibility rates are above the threshold, they calculated, each child that gets the vaccine will not only be protected

advantage is, you don't have to pay your own airfare," he smiles.

More recently, Wallinga and his colleagues touched another hot-button issue: the threat of a new flu pandemic. This time, while other research groups were predicting a pandemic flu virus to spread like wildfire, with every patient infecting up to 17 others, RIVM modellers were early with less dire predictions. Based on historical records, they projected about 1.5 secondary infections from every patient. Again, Wallinga says, by the time they were ready to publish, other researchers had beaten them to the finish line. "We got a footnote in Nature," he says, "but colleagues know who were among the first. These days we get many requests to join

Sometimes, the team is more lucky. In 2005, Wallinga's work on measles bore fruit with a paper in PLoS Medicine (see sidebar). "We've always published regularly," Wallinga says, "and it's nice to see medical journals getting more interested. It's easier to get papers accepted now, although it's still a gamble. In the end, publishing is just nice, like a pat on the head. The real kick comes from suddenly spotting order in seemingly chaotic numbers. The rest is just a circus in which you have to play along."

"At the moment, we're doing well. In 2003 I was working on my own, now there's seven of us. It's like the start of an epidemic. Let's hope it doesn't die down, as most epidemics eventually

> him- or herself but will also prevent 0.61 other cases in a subsequent major outbreak, clearly demonstrating the public health dimension of measles vaccination. The authors point out that inThe Netherlands, the threshold was crossed in 2003. Without additional vaccination efforts, they say, the risk of a major outbreak is real and will continue to grow.

> The findings may be relevant to all countries with high vaccination rates, as well as countries hoping to attain them in the future. Keeping the fraction of susceptible individuals below the threshold may be the key to averting major measles outbreaks.

Wallinga J, Heijne JCM, Kretzschmar M A Measles EpidemicThreshold in a Highly Vaccinated Population PLoS Medicine, Nov 2005, Volume 2, Issue 11, pp. 1152-1157.

DOI: 10.1371/journal.pmed.0020316

# Reaping the profits of what has been sown



Bas Bueno de Mesquita, Nutrition, Medicines and Consumer Safety Division (RIVM-VGC) In the early 1990s, RIVM joined international cohort studies on lifestyle habits and chronic diseases like cancer. In 2005, an interim analysis confirmed that high meat consumption is associated with an increased risk of colorectal cancer. Over the next few years, frozen blood samples will shed much more light on such risks.

Bas Bueno de Mesquita started his career as a tropical doctor. For five years, he was stationed in a leprosy hospital in India, at one point delivering basic health care to 40,000 rural inhabitants by truck, and later helping local villagers improve the way they cultivate rice and maize.

Having seen extreme poverty changed Bueno de Mesquita's outlook on life, and on the purpose of research into western lifestyles and chronic diseases. "Those people maintained their pride and self-respect while working hard to improve their lives," he says. "So I reject the idea of low-income groups in rich countries being pitiful and not able to take responsibility. The only dignified way to deal with unhealthy lifestyles is to investigate the risks and then to inform people. If alcohol increases a woman's risk of getting breast cancer, then she should have access to that information, since to prevent is so much better than to cure. To that extent governments bear a responsibility, and I hope to contribute to that. But in the end, it's up to people to decide themselves."

# Many papers

Bueno de Mesquita's career took a sharp turn when in 1982, after studying public health at Johns Hopkins University in Baltimore (US), he failed to secure a new work permit for India, where he was set to start teaching at a university. Wondering whether he should take up his old job as a physician, he accompanied his former professor in social medicine to a meeting of the International Agency for Research on Cancer (IARC) in Lyon (France). He has been working on cancer and lifestyle ever since.

"My work at RIVM basically spanned three large IARC projects," Bueno de Mesquita says. The third and biggest study, the European Prospective Investigation into Cancer and Nutrition (EPIC), will probably keep him busy for the remainder of his career, he adds. Co-ordinating the largest of two Dutch cohort studies, analysing questionnaires, health records and blood samples of close to 23,000 people, and co-authoring papers based on that mountain of data, consumes virtually all his time.

Apart from generating many research papers, international collaborations have another important advantage, says Bueno de Mesquita: They help prevent the confusion caused by many separate, smaller and often contradictory epidemiological studies. "Testing hypotheses in many centres across many countries shows right away whether results are consistent," he says. Sometimes, he adds, researchers have touted findings to the general public that should have been replicated first.

More solid conclusions may also come from the millions of blood samples currently frozen in liquid nitrogen. They were taken at the time people were enrolled in cohort studies and have

been meticulously kept ever since. For the RIVM cohorts, half of the samples are stored at the Bilthoven campus, while backups are kept in Lyon. "Right now there is a boom in research papers based on questionnaires, which mostly generate weak epidemiological associations," says Bueno de Mesquita. "In the coming years I expect a strong upsurge in papers based on biochemical and genetic markers found in those biological samples." Such studies could eventually help assign risks to individual people and their personal lifestyle decisions. "Last week I took part in a teleconference on pancreatic cancer with the US National Cancer Institute," he adds. "They will analyse genes in samples taken from large international cohorts, including EPIC. Genomics will increasingly be integrated in epidemiological research. After that there will be proteomics, where we will be looking at patterns of proteins in the blood, and then metabolomics, focusing on metabolites. And all of that will only make sense when lifestyle factors are also taken into account. So there's a lot left to be done, and I hope to be able to take part in much of it in my remaining eight years at the institute."

To Bueno de Mesquita, these new research opportunities underscore a key point: RIVM will need to maintain its collection of blood samples for many years to come. "Public investments in the 1990s have filled this great repository," he says. "It would be very unfortunate if we would not be able to reap what we have sown."

# Eating red meat associated with higher incidence of colorectal cancer

The European Prospective Investigation into Cancer and Nutrition (EPIC) was initiated in 1992. Supported by the European Commission, the World Health Organisation and the International Agency for Research on Cancer, it is one of the largest prospective studies ever undertaken into the relationships between diet, nutritional status, lifestyle, environmental factors and the incidence of cancer and other chronic diseases. More than 500,000 people in ten European countries were questioned and had blood samples taken at the time of enrolment. Their health status has been monitored ever since.

In The Netherlands, more than 40,000 subjects entered EPIC between 1993 and 1997, just over half of them through RIVM's MORGEN-EPIC study, co-ordinated by Bas Bueno de Mesquita. (The other half enrolled in PROSPECT, a study co-ordinated by Petra Peeters at Utrecht University.) In June 2005, researchers published an analysis of the relationships between consumption of processed and red meat and fish on the one hand

and the riskof developing colorectal cancer on the other.

The analysis showed that, as had been predicted, people with diets rich in processed and red meat develop colon or rectal cancer more often than those with low intakes of these products. The relationship was consistent across culturally diverse countries such as Greece, Spain, and The Netherlands.

The analysis suggests that an average 50-year-old who eats relatively large amounts of red meat has a 1.7% chance of developing colorectal cancer over the next 10 years, while for someone consuming relatively little red and processed meats, that chance is 1.3%.

NoratT, Bingham S, Ferrari P, Slimani N, (...), Bueno de Mesquita HB et al.

Meat, Fish, and Colorectal Cancer Risk: The European Prospective Investigation into Cancer and Nutrition. Journal of the National Cancer Institute, Vol. 97, No. 12, June 15, 2005, pp. 906-916. DOI: 10.1093/jnci/dji164

# Will baby boomers stay healthy longer than their parents?

At the request of the Dutch ministry of Public Health (VWS), RIVM's Centre for Public Health Forecasting publishes a prognosis of the country's future healthcare needs every four years. Fundamental research helps lay the foundations.



Johan Polder, Public Health and Health Services Division (RIVM-V&Z) Johan Polder was trained as an economist. Unlike most of his college peers, he says, he was never attracted by courses in business administration, accountancy, or fiscal regulation. Macro-economic and institutional questions excite him much more. After graduating, he found his calling through his Ph.D. thesis, aptly titled 'Cost of illness in The Netherlands'. When he was asked in 2002 to join RIVM's Centre for Public Health Forecasting, Polder says, he asked for two things: full independence from policy makers, and a greater emphasis on scientific rigour. Both wishes were granted.

As to the centre's independence, Polder says, that's demonstrated by the conclusion, in last year's Primary Care report (see sidebar) that making patients pay small deductibles for primary care will not really reduce their demand, as many Dutch politicians hoped. With regard to scientific rigour, Polder says, researchers at the centre are constantly challenging each other to aim for the highest standards. "We ask each other: Did you use the right data and methods? Was your literature search sufficiently comprehensive?" The Centre, Polder says, is built on two pillars. One consists of policy-oriented research, designed to help policy makers evaluate old policies and design new, more effective ones. The second pillar is fundamental scientific research, aimed at understanding the demographic and epidemiological forces that will shape future healthcare systems.

"It is like having two legs," Polder says; "I would not want to stand on just one of them.

# **Red Herring theory**

In science, Polder says, he still gets most excited by large-scale economic questions. He is fascinated, for instance, by the fact that we don't really know the effects of ageing populations on future healthcare costs. "Will costs rise? If so, to what extent? Will future 70-year-olds require as much healthcare as current 70-year-olds? Or is absolute age really not important, as Peter Zweifel's 'Red Herring theory' postulates, while proximity of death is? If that's true, then healthcare expenses would merely shift, not rise."

Polder has tested the Red Herring hypothesis using Dutch healthcare registries. The theory has some merit, he found, but it is not completely right. As is always the case in science, new research questions flowed from the analysis. Do different age cohorts have different healthcare demands? Will baby boomers stay healthy longer than their parents did because they enjoyed greater prosperity? If so, what does that mean for the future costs of healthcare? "I'm writing a research proposal to further look into those exact questions," Polder says.

At this point, Polder says, it would be classified as fundamental research, supported by RIVM's strategic research program and carried out in co-operation with universities such as Tilburg and Rotterdam. "Yet it could become very relevant for the 2010 edition of our policy-oriented

prospects," he says. Being part of the research cor of science and policy, Polder and and new ideas are floated at a strive to participate in the sci like writing, and I get a real k it's good for RIVM to be seen Not everyone outside RIVM's says. "Recently one of my form thought that we don't do read is wrong. Obviously, we're no splendid isolation. Yet we have environment. And I myself ha

# The future of primary care in The Netherlands

Primary care in The Netherlands is facing rapid changes. The country's population ages while new types of care providers are reshaping the field. Also, rising healthcare costs prompt the Dutch government to seek regulatory changes.

This study, carried out jointly with the Netherlands Institute for Health Services Research (Nivel), aimed to assess all these developments and produce an integrated projection of demand, supply and organisation of primary care in 2020. It also predicted chances of success for potential policy measures.

The report concludes that overuse of primary care has diminished to a low level in 2005. Attempts to further curb unnecessary use will fail unless very high deductibles are introduced that cannot be reinsured. The recent restructuring of Dutch health insurance will not significantly affect demand.

Curbing demand through increased prevention will only work short-term. In the long run, prevention will increase demand for primary care, because preventive measures are often implemented by primary care givers. Moreover, prevention causes further ageing which in turn will lead to a higher prevalence of chronic disorders like asthma and diabetes and to more injuries, all increasing demand for

Being part of the research community is important if RIVM wants to keep bridging the worlds of science and policy, Polder says. "Most debates these days play out on the international stage, and new ideas are floated at big conferences. We translate these to policy makers but also strive to participate in the scientific debate ourselves by publishing in peer-reviewed journals. I like writing, and I get a real kick out of seeing our papers printed and used in the field. I think it's good for RIVM to be seen as a real partner in the academic world."

Not everyone outside RIVM's walls is familiar with the institute's high-quality research, Polder says. "Recently one of my former university colleagues, after a couple of drinks, told me he thought that we don't do real science at RIVM. I was flabbergasted. It made me think, but he is wrong. Obviously, we're not a university. You won't find people here who keep digging in splendid isolation. Yet we have brilliant scientists for whom RIVM provides a very inspiring environment. And I myself have published one of my best papers while at this institute."

primary care. These trends will offset demand reductions thanks to the prevention of back and neck complaints. Rising numbers of part-time practitioners will require more large-scale providers.

Between 2005 and 2020, supply of general practice is expected to grow by 11.5%, yet demand will increase by 13% to 20%. The predicted shortage is less severe than in previous studies because primary care has become more efficient. Efficiency could grow further if more tasks are entrusted to assistants and nurse-practitioners, and primary mental healthcare is strengthened further. Serious shortages of nurses are projected because of sharp rises in home care.

Bakker DH de, Polder JJ, Sluijs EM, Treurniet HF (eds) Public health forecast for primary care in The Netherlands in 2020.

["Op één lijn -Toekomstverkenning eerstelijnszorg 2020"]. Part of series: 'Public Health Status and Forecasting 2006' (www.rivm.nl/vtv) RIVM Report 270751009/2005 ISBN 9031346195

www.rivm.nl/bibliotheek/rapporten/270751009.pdf

# Just a few chemicals are causing most of the problems

Environmental risk assessment often means dealing with many uncertainties; we know very little about the tens of thousands of chemicals floating around. How to make the best use of what we do know?



Dik van de Meent, Environment and Safety Division (RIVM-MEV)

Dik van de Meent was trained in organic geochemistry at the University of Delft. Even as a student, he was curious about the environmental impact of man-made chemicals, whose number was rapidly growing. As an 'environmental chemist' at the university, Van de Meent tried to understand the behaviour of chemicals in the environment. To assess their longrange effects he helped build mathematical models in which chemicals moved between soil, freshwater, groundwater and the atmosphere.

Van de Meent's early work landed him a job as an environmental toxicologist at the Dutch National Institute for Drinking-water Supply (Rijksinstituut voor Drinkwatervoorziening), which merged into RIVM in 1984.

Van de Meent has fond memories of those early days. Working in a small institute, he says, often meant counselling policy makers very directly. He remembers being called into the office of Hans Könemann, who in the early 1980s headed the department of chemical substances at the Ministry of Public Housing, Spatial Planning and the Environment (VROM) and would later join RIVM. Könemann had a problem: A new law would oblige companies to report their new chemicals, after which the government had to quickly assess their environmental impact. He had no idea yet how to handle those reports.

"I remember telling him: 'One fool can ask more questions than seven wise men can answer'," says Van de Meent . "Afterwards, my boss had to save me from trouble."

For Van de Meent, the meeting became a turning point. "Könemann said: 'You can stay up in your ivory tower dealing with many scientific uncertainties, or you can come down and help me build a system that works.' With those words he converted me. We may not yet know everything about a situation, but that shouldn't keep us from using what we do know. If only nanograms of a compound are likely to be in the water, while grams are needed for toxic effects, then it's not a priority for regulation. In a way, that meeting ultimately led to the paper we finished in 2005" (see sidebar).

# Setting priorities

Over the past decades, many thousands of new chemicals have been introduced into the environment. Regulating them all to prevent harm is still a huge challenge, since very little is known about most of them. "The million dollar questions are how to quantify the environmental risk of all those chemicals together and to help governments set the right priorities."

For Van de Meent the big surprise came when he found that, at least mathematically, a tiny fraction of all chemicals is probably responsible for most of the environmental risk. "Our simulations suggest that 95 percent of the toxicity comes from just 5 percent of all chemical compounds. We just don't know yet which ones. That really opened my eyes, although,

looking back, I should have known it all along," he says. "To my mind, the message to governments is clear: Instead of regulating 10,000 chemicals, we should probably focus our efforts on quickly identifying the 500 most important ones." Understandably, Van de Meent says, his clients are not overly interested in basic research questions like these; they have to work with the regulation as it has been enacted, and mathematical simulations usually don't solve their problems. As a result, it can be difficult for RIVM scientists to find the time to finish such research. That's why Van de Meent relishes his collaboration with Radboud University Nijmegen, where he has been a part-time professor since 2002. "I laid the groundwork for this research during my sabbatical in Osnabrück, Germany," he says, "but it was thanks to Jasper Harbers, a graduate student from Nijmegen, that we could finish this paper quickly. And it got published in Environmental Science and Technology - the highest-impact journal in the field."

# Finding the needles in a chemical haystack

In Europe, more than 103,000 man-made chemicals are registered at the European Chemicals Bureau. Most of them are currently exempt from regulation since they were on the market when rules were introduced. Extensive toxicological data is available for only a small fraction, so worries remain about the thousands of chemicals about which we know very little.

The European Commission has proposed new legislation for Registration, Evaluation and Authorisation of Chemicals (REACH), which could come into effect as early as 2007. Industries would have to document the toxic effects of about 10,000 chemicals, both old and new.

Van de Meent and his colleagues collected data on 343 high-production chemicals reaching North Sea ecosystems. They calculated the so-called 'toxic pressure' of all those chemicals combined, and then tried to estimate the individual contribution of each one based on production volumes, emission rates, chemical structure, persistence, bio-reactivity, and so on.

Getting reliable estimates for individual compounds proved impossible because of the many uncertainties. By modelling

these uncertainties in a computer, however, they were able to estimate the overall toxic pressure much more reliably. The researchers went on to study the impact of the Pareto Principle, according to which 20 percent of any group will typically cause 80 percent of the effect. Statistically, they found, 83 percent of the chemicals can be expected to contribute only negligibly (less than 0.1 percent) to the overall toxic pressure, while the remaining 17 percent will be 'possibly relevant'.

Such calculations, the authors suggest, could lead to more cost-efficient ways to monitor and regulate the release of chemicals. Rather than spread research and regulation efforts evenly over all chemicals, governments could try to pinpoint the small number of compounds that have the most profound environmental effect.

Harbers JV, Huijbregts MJ, Posthuma L, Meent D Van de Estimating the Impact of High-Production-Volume Chemicals on **Remote Ecosystems by Toxic Pressure Calculation** Environmental Science & Technology, Vol. 40, No 5, pp. 1573-1580 DOI: 10.1021/es051633m

# Four thousands steps on a typical workday

To combat rising overweight and a growing lack of exercise among its citizens, the Dutch government wants to promote physical activity. A large-scale intervention program could bring significant health gains at reasonable costs, researchers have found.



Wanda Vos and Wanda Bemelmans Public Health and Health Services Division (RIVM-V&Z)

Wanda Bemelmans and Wanda Vos are often called 'the two Wandas'. They both studied nutrition at Wageningen University; they both bike to work from Zeist, a residential town six kilometres south of the RIVM campus; and upon arrival, they walk up to adjacent offices. To the outside world, such similarities can be confusing - especially because both ended up doing research for the same report. "Some people got lost looking for the right Wanda, but since we're next-door neighbours, that was easy to clear up," both Wandas say. Wanda Vos was a dietician when she joined RIVM in 1997. She became a researcher and earned her Ph.D. degree in 2004 after studying the health aspects of physical exercise. Wanda Bemelmans joined RIVM in 2002 after finishing her doctoral thesis on lifestyle-counselling for high-risk patients. Together, they proved to be the perfect couple to co-ordinate a comprehensive, first-time study into the costs and feasible health gains of a national campaign promoting exercise.

# Shocked

Researching the blessings of exercise and training has made them more conscious of their own behaviour, the Wandas say, and made them realise how difficult it is to meet the Dutch Standard for Healthy Exercise: More than 30 minutes of moderate exercise at least five days a week. Bemelmans frequently takes weekend hikes, she says, but that isn't enough. Vos used to visit the health club twice a week, but hasn't picked up the routine after returning from maternity leave. She also used to do ballroom dancing, but that habit has waned, too. "For a long time, I thought I was easily getting my 10,000 steps a day," says Bemelmans. "When I finally used a step counter, I was quite shocked to learn that I barely reached 4,000. It's disappointing to realise how little exercise you get on a typical workday." Luckily for both, they still have their 20-minute bicycle commute. "Thanks to that, I'm still complying with the norm," says Bemelmans.

While both really enjoy doing scientific research, combining the work with other commitments can be challenging, they say. In recent years, they have sensed a tendency to move towards performing meta-analyses and compiling research published by others. "In the long run, that could harm our capacity to do high-quality research," says Bemelmans. Gathering your own data makes it a lot easier to publish papers and establish a scientific reputation, adds Vos.

Both researchers are brimming with plans for new research projects. Vos, fresh from maternity leave, is contemplating a study into how social environment affects exercise behaviour, a subject also topping international research agendas. Bemelmans has secured funding from the Netherlands Organisation for Scientific Research (ZonMw) to study the efficacy of computerdeveloping cardiovascular disease. wouldn't harm either."

# Exercise plan would save lives at moderate cost

As part of a strategy to combat rising obesity and overweight, the Dutch Ministry of Health, Welfare and Sport (VWS) plans to launch a National Action Plan for Sport and Physical Activity. The authors set out to give the plan scientific underpinnings and to calculate the cost-benefit ratio in euros per life year gained.

Comprehensive research of the literature and an inventory of expert opinions and experiences from local programs produced key factors and conditions determining the chances of success. Any plan should use an integrated approach and secure support and operational assistance of all relevant stakeholders, the authors conclude. Groups that can be targeted selectively should be identified and scientific research should be part of the plan. Based on analyses of two Dutch pilot projects, the authors defined feasible objectives of a National Action Plan. After five years, they say, such a plan could reduce the prevalence of inactive individuals (currently at about 8%) by one or two percentage points, and the prevalence of overweight (currently at about 47%) by one to three percentage points. Implementation would

aided lifestyle counselling. She's also considering writing a proposal to use blood samples from one of RIVM's cohort studies to find bio-markers that can predict obese people's risk of

Meanwhile, both are still riding the wave of their successful cost-effectiveness study. "We scored points internationally," Bemelmans says. "It has become easier to give workshops and presentations, and I've been invited to a working group at the World Health Organisation." The researchers have submitted adapted versions of the report to several peer-reviewed journals. Says Vos: "As researchers, we also have a personal reputation to uphold. We liked putting out a colourful RIVM report, but publishing in the New England Journal of Medicine

cost approximately € 94 million per year or € 6 per capita. Meeting the plan's objectives would prevent tens of thousands of cases of cardiovascular disease, diabetes and cancer over the next twenty years, which would save many lives. Every life year gained, the authors calculated, would cost somewhere between € 6,000 and € 6,500. Added quality-adjusted life years (QALY) would cost between € 5,600 and € 6,100 – amounts well within generally accepted boundaries for health interventions, they conclude.

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# Tiny particles having large health effects

Much confusion arose in 2005 when new, EU-mandated limits for peak concentrations of particulate matter went into force. Refining such standards and understanding the health effects of small particles in ambient air will take many years of research.

Flemming Cassee was trained as a biologist and earned his Ph.D. at Utrecht University after studying the health effects of inhaling aldehydes. Following a few years at the Dutch institute for applied research (TNO) in Zeist, he moved to RIVM in Bilthoven, also close to Utrecht, in 1995.

Cassee now heads RIVM's section of Toxic Effects of Air Pollution, where he still does inhalation research. Part of that work is done in RIVM's unique mobile lab, a trailer in which human volunteers can be exposed to various concentrations of particulate matter in air sampled at remote high-risk locations such as highway roadsides.

In 2005, Cassee found himself in the eye of a political storm after the implementation of new EU rules on maximum levels of particulate matter. Overall levels in the Netherlands had fallen for many years and still continued to decline. But to the public at large, the introduction of lower limits for peak loads suggested they were rapidly rising instead. The new measures caused many major building projects to be put on hold, leading to intense legal and political wrangling and a flurry of media reports. Ultimately, the Dutch government decided to take sea salt particles, blown in from the North Sea, out of the equation – a pragmatic solution that isn't necessarily evidence-based, Cassee notes.

In an attempt to stem the confusion, Cassee, together with the Netherlands Environmental Assessment Agency, authored a comprehensive report, entitled 'A closer look at particulate matter' (Fijn stof nader bekeken).

Halfway 2006, the political dust has mostly settled. What's left are the many news clippings covering Cassee's office walls.

# Peer-reviewed

When Cassee arrived at RIVM, he says, reports used to be his department's main outlet - papers in peer-reviewed journals were published only occasionally. Cassee has worked hard to turn that situation around. Today, he says, his department produces as few reports as possible. "In general, gray literature, including reports, is no longer cited in reviews by the US Environmental Protection Agency (EPA) or the World Health Organisation," he says. "Our work has to be peer-reviewed."

Cassee doesn't regret the transition. Writing reports is often time-consuming because many people like to have their say, he says, while research papers only need the consent of coauthors and, if the subject is politically sensitive, his boss. What's more, he adds, reports don't show up on PubMed, an international, web-based database for life-science-related papers. Cassee has published papers in highly respected journals in the field of toxicology, aerosol research, epidemiology and environmental exposure. "Personally, however, I don't have strong papers," he says.

own strategic research fund (SOR) and sources outside. field - in Europe, the US and Japan." and TNO in our own country," he says.

# Hypertensive rats can be models for susceptible humans

The health consequences of airborne particulate matter are of major concern because epidemiological studies have shown effects at concentrations often observed in ambient air. Increased concentrations of particulate matter have been linked to increased hospital admissions, visits to emergency rooms, and even premature deaths. Health effects have also been observed in animal research and inhalation studies using human volunteers. Not only the respiratory tract is affected; cardiovascular disease, too, appears to be an important consequence of exposure to particulate matter

Much research will be needed, however, to understand these relationships and to compare the effects of ambient air at different locations.

This study, part of two multi-centre EU-funded research projects, aimed to determine which dose should be used in animal testing and how long after exposure necropsies on the animals should be performed. The study used rats prone to hypertension to guarantee that effects are picked up, and to simulate susceptible humans.



Flemming Cassee, Environment and Safety Division (RIVM-MEV)

preferences on which journal we publish in, as long as our peers and the public can find our

Being involved in experimental and field research is essential for RIVM, Cassee says, although policy questions will always be the starting point. Luckily, he says, his main client, the Ministry for Housing, Spatial Planning and the Environment (VROM), agrees that broader research has a place within its assignments. More fundamental research, Cassee says, is funded by RIVM's

Even those two sources cannot answer all the needs of an ambitious research group. That's not a bad thing, Cassee says. "Our limited capacity has forced us to collaborate with colleagues abroad. Thanks to that, we now have strong partnerships with all the important players in the

Having seen examples world-wide, Cassee likes the set-up of the US EPA. "EPA has a strong research programme on air pollution. What's more, EPA also funds external research, enabling it to influence science agendas elsewhere," he says. Cassee helped EPA review joint research programs of US universities and institutes. "I'd love to set up similar projects with universities

The next few years Cassee hopes to clear up how particulate matter produces health effects. "Thus far we've done mostly association studies in which all particle types and sizes were added up," he says. "We have learned a lot about the complexity of particulate matter, but for more source-oriented abatement strategies we need to know what goes on underneath. Do particles enter the body only through the lungs, or can they also enter through nasal passages? Which type causes which health effect? What's the role of particles smaller than one hundred nanometres, which currently are not regulated at all? Are peak exposures very important or should we focus on long-term exposures? Those are the questions that really get us excited."

> Air taken from a road tunnel was injected directly into the trachea of the rats at various concentrations. For this breed of rats, the optimal testing dose lies between three and ten milligrams of particulate matter per kilogram body weight, the researchers found. Necropsies to check for health effects are best performed 24 hours after exposure. Among the health effects seen were pulmonary inflammation, oxidative stress and, possibly, changes in blood circulation. Spontaneously hypertensive rats are good models for assessing possible health effects of particulate matter in humans, the researchers conclude.

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# Fighting microbes without borders

A world-wide epidemic of tuberculosis is raging, and strains of the microbe that are resistant to drugs and a widely used vaccine are emerging. Recognising these strains is the first step in understanding the epidemic-and ultimately defeating it.

Kirsten Kremer used to dream about leaving her country and going to Ethiopia, to fight poverty and tropical diseases where they occur. But the plan fell through; instead Kremer now contributes to the fight from the RIVM campus in Bilthoven. From 2000 to 2003, she managed an international effort to find the best way to identify separate strains of Mycobacterium tuberculosis, the causative agent of TB, a disease that kills nearly two million people worldwide annually.

Thanks in part to Kremer's research, there now is a new standard test for discriminating between different M. tuberculosis strains; it produces reliable results in less than a day, rather than several weeks. What's more, thanks to these tests researchers are now homing in on why some tuberculosis strains evade the current TB vaccine more easily than others. Such knowledge could help researchers find new, better vaccines.

# Genetic fingerprinting

Kristin Kremer's career path at RIVM was unusual. She didn't start out as a researcher; in 1993, after graduating from the Institute for Life Sciences and Chemistry, she became a lab technician at RIVM's Diagnostic Laboratory for Infectious Diseases and Perinatal Screening. There, she performed genetic fingerprinting techniques.

Thanks in part to her being fluent in English, Kremer quickly found her way into international collaboration projects. In 2000, the lab initiated a new research project funded by the European Commission (EC), and Kremer's boss, Dick van Soolingen, co-ordinated the contributions from 32 participating labs. Kremer became the project's manager, a perfect position for setting up research for a Ph.D. thesis.

And as it turned out, the project also gave her ample opportunity to fulfill her desire to spend time abroad. "I enjoy being in touch with people all over the world," Kremer says. "Our lab has a good reputation, and people ask me all sorts of questions about genetic fingerprinting. It's great to be able to help them out quickly."

She loves doing research, but it often has to be combined with other assignments, Kremer says. Recently, for instance, she has taken over a few management tasks; she's also filling in for a colleague who coordinates the diagnostic analysis of Mycobacterium samples, which routinely come in at a rate of about 1,500 per year. "Diagnostic testing always comes first," Kremer says. And she doesn't regret it; it's nice to work on real patients, people with names and histories, once in a while.

Besides, the daily routine can also spawn new research. "In 1997, for example, we characterised a new Mycobacterium species from a two-year-old Somalian patient." After earning her Ph.D. in 2005, Kremer quickly moved on to new international research projects. RIVM will co-ordinate a new EC-funded project called TB-ADAPT, in which eleven labs will take a very close look at genetic variation among M. tuberculosis strains. The goal: to find specific spots in the genome that affect resistance against vaccines or drugs. Because

many previous studies focused on Europe and Asia, Kremer plans to do more testing on strains emerging in Africa and South-America. (She's already looking forward to the meetings abroad.)

although I confess we had tried The Lancet first." hope I will be able to contribute to that."

# Beijing strain may be evading TB drugs and vaccines

Although tuberculosis (TB) has all but disappeared in rich countries, the disease is still raging world-wide. The World Health Organisation (WHO) estimates that one-third of the world's population is infected with Mycobacterium tuberculosis, TB's causative agent. Many of them, especially those who are also carrying HIV, will eventually become ill. In 2004, according to WHO figures, 9 million people got sick and 1.7 million died of TB, with death rates highest in Africa and Southeast-Asia.

Hampering the battle against the bacillus is the appearance of strains that have become resistant to either anti-

TB drugs or Bacille Calmette-Guerin (BCG), a partially effective vaccine used in many countries. Learning how to quickly and reliably distinguish TB strains is important for understanding the epidemic and devising new control strategies.

As part of a European research project Kremer worked with 30 other labs to compare 21 DNA fingerprinting tests. All labs characterised 131 unmarked isolates, 62 of which were doubles. Two tests topped the list with equal reproducibility and discriminatory power, the researchers found.

Kristin Kremer, Centre for Infectious Disease Control (RIVM-CIb)

Another advantage of the collaboration project is that there's an emphasis on fundamental research, leading to many opportunties to publish in peer-reviewed journals. "To me, that's very important," Kremer says. "Apart from one yearly report on the state of TB in The Netherlands, these days we try to publish in international journals. That way, everyone can read what we've done. And yes, I prefer to publish in high-impact journals; I think every researcher should aim for a paper in Science or Nature. But of course it usually doesn't work that way. We just had a paper published in Emerging Infectious Diseases, which was great,

Next on Kremer and Van Soolingen's list: applying for a grant from RIVM's strategic research fund to have the genomes of about twenty TB strains fully sequenced. That, too, could prove invaluable for the development of a new, improved, and affordable vaccine, which many scientists agree is the world's best hope to halt TB in poor countries. Says Kremer: "I really

> Kremer then checked 49 studies world-wide for the occurence of the so-called M. tuberculosis Beijing strain, first described in Beijing in 1995 but found all over the world since then. The strain is now dominant in Southeast Asia and some parts of Russia, while in Western Europe its impact is still small but growing.

Finally, Kremer and colleagues applied the best fingerprinting techniques to analyse two subtypes within the Beijing strain. Only one of these, dubbed the 'typical Beijing strain', proved to be associated with vaccine and drug resistance. It was also more prominent in younger patients. The findings add weight to the theory that the Beijing strain is the microbe's adaptive response to the current generation of TB drugs and vaccines.

### Kremer K

Genetic markers for Mycobacterium tuberculosis; characterisation and spread of the Beijing genotype (Ph.D. thesis) ISBN 90901955521

# The exploding field of medical nanotechnology

Triggered by developments in science, RIVM set out to take stock of the potential health risks of emerging nanotechnologies. Researchers at the institute are preparing to extend their own work in the budding field.

Robert Geertsma was trained in organic chemistry - back at the University of Twente, he considered switching to courses in medical materials but decided against it. Yet at RIVM he ended up at the Medical Technology Section, and he now is a senior author of two comprehensive reports on medical applications of nanotechnology.

The irony isn't lost on him, but Geertsma says he's hardly the only one who ended up switching to nanotechnology. He cites the example of David Reinhoudt, his university mentor, who now chairs the board of NanoNed, a Dutch research and development initiative dedicated to nanotechnology.

A few years ago, Geertsma approached the Ministry of Health, Welfare and Sport (VWS) with the idea of identifying potential health risks of this emerging technology. His international contacts told him a lot was happening, Geertsma says, and the government agreed it was time to take stock of developments and start thinking about potential problems.

The results of the study, written jointly with Boris Roszek and Wim de Jong, surprised him, says Geertsma. "Nanotechnology has already developed further and more widely than I had ever imagined," he says. "That is also the key message in these reports: the technology is booming and in medicine it's already being applied today. We urgently need more toxicology research because, apart from the fact that nano-particles can be highly reactive, we don't really know very much about the risks."

# Dig deeper

On a scale ranging from policy advisor to bench scientist, Geertsma describes himself as somewhere in the middle. His lab experience dates back to his university years, which ended in 1994. At RIVM, his main clients are policy departments at the health ministry and the Dutch Health Care Inspectorate (IGZ), both of which are focused more on 'desk research' than on experimental studies.

For their investigation of the state of the art and the risks of nanotechnology, Geertsma and colleagues researched the scientific literature, examined company websites and attended scientific conferences. The study resulted in two reports, both of which made his clients happy. They're now used internationally to summarise the issues in the budding field.

Yet Geertsma himself would have liked the opportunity to delve just a little bit deeper, and redraft the reports into full-blown research papers that could have been submitted to peerreviewed journals. Finding the time to do that, however, isn't easy, he says. In recent years, Geertsma says, it has become more difficult to convince policy makers at the health ministry that RIVM researchers sometimes need to dig deeper than the policy question at hand. Being intimately involved with the research itself, Geertsma says, will nevertheless be

Netherlands to chair a working group on the topic." research partners outside.

# More data on nano-particles' toxic effects needed

Nanotechnology is the design, characterisation, production and application of structures, devices and systems by controlling the shape and size of materials at the nanometre scale. (One nanometre is one-millionth of a millimetre.) In two reports, published simultaneously in 2005, RIVM presented an overview of current and future medical applications of the technology as well as an assessment of its risks for human health

In medicine, the first report says, the impact of nanotechnology will be profound, ranging from diagnostics to therapy and tools for prevention. Some types of nanotechnology are already in use, for instance in surgery, medical imaging, and tissue engineering. Examples include nano-structured surgical blades and suture needles. reinforced with stainless-steel. Other applications are found in contrast-enhancing agents for magnetic resonance imaging, bone replacements, wound dressings, antimicrobial textiles, in-vitro molecular diagnostic chips, micro-cantilevers, and micro-needles. In the next few years, many other applications will hit the market, in particular in surgery, cancer diagnosis, cancer therapy, bio-detection of disease markers, molecular imaging, implant technology, tissue engineering, and devices for drug, protein, gene, or radionuclide delivery.



Robert Geertsma, Nutrition, Medicines and **Consumer Safety Division** (RIVM-VGC))

important for RIVM's ability to stay in touch with the principal scientists in the field. "If you do research yourself, you are better able to assess the importance and quality of other people's work, even if it's in a neighbouring field," he says. "At conferences, people approach you differently if you present your own data." He cites the example of Wim de Jong, his co-author and RIVM colleague, who is well known internationally because of his experimental work. RIVM's unique position as a public health institute that actively participates in research programs has benefited policy clients, says Geertsma. For instance, when he represents the Dutch government in European Union committees, strong ties with research have helped put The Netherlands on a par with bigger member states like France, Germany, and the UK. "In 2004, the Dutch government used our scientific input to place emerging medical technologies high on the agenda in Europe," he says. "Subsequently, the European Commission asked The

Many more chances for in-depth research may be just around the corner. Researchers from several RIVM departments have joined hands to set up a Nanotechnology Safety Centre. Funded by internal as well as external sources, they plan to collaborate extensively with

> Still, not much is known about nanomaterials' potential toxic effects, the second report says. Free-floating particles in the nanometre range in particular warrant research, since very small particles tend to be much more reactive than bigger ones with the same chemical composition. Therefore, relying on existing toxicological data will not be sufficient. Special attention should be given to drug-delivery systems that release nano-particles or nano-tubes inside the body. Regulatory guidance at European levels is recommended, as is further research into nanotoxicology.

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# Research Output

# Research output

# Centre for Infectious Disease Control

CIb

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# Professorial Chairs

#### Kromhout D

Professor of Public health research Wageningen University and Research Centre

#### Loveren H van

Professor of Immuno-toxicology University of Maastricht

#### Slob W

Professor of Toxicology Utrecht University Steeg H van Professor of Toxico-genetics Leiden University

Stephany R Professor of Food of animal origin Utrecht University

# Vos J

Stolker AAM

Professor of Toxicological pathology Utrecht University

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