
Health Council of the Netherlands Reports 2008

Executive summaries



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Health Council of the Netherlands

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The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, Agriculture, Nature & Food Quality, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.



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Preface

The Health Council of the Netherlands (Gezondheidsraad) is the scientific advisory body on health and health care to the Dutch Government. Since the integration, in February 2008, of the Advisory Council on Health Research (RGO), the Health Council also advises on health (services) research. Its recommendations cover fields which relate to the health of the population, such as clinical medicine, public health, environmental protection, food and nutrition and occupational hygiene. The Council's advisory reports are usually drawn up by independent, multidisciplinary committees of experts.

The present volume is a compilation of the executive summaries of reports published in 2008. Other publications without a summary are mentioned in Annex A. Copies of all reports, however, can be downloaded from our website: www.healthcouncil.nl or www.gr.nl. When ordering please mention the publication number.



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Contributing to the optimisation of health care

Health care for the elderly with multimorbidity

Health Council of the Netherlands. Health care for the elderly with multimorbidity. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/01. ISBN: 978-90-5549-685-3 (in Dutch)

The request for advice from the State Secretary

This report concerns multimorbidity amongst the elderly. Multimorbidity is the co-occurrence of diseases, irrespective of the nature of their relationship. Multimorbidity occurs in all ages, but mostly in the elderly. In the coming years the proportion of elderly people in our society will increase rapidly, and as a result the number of elderly people with multimorbidity will increase as well.

This led the State Secretary for Health, Welfare and Sports to request the Health Council of the Netherlands to advise her on multimorbidity in the elderly and on how to develop an effective geriatric service for elderly people with multimorbidity.

Multimorbidity is common among the elderly

Around two-thirds of all over-65s have two or more chronic diseases, and this percentage increases with age. Amongst people over 85 years of age, at least 85% have more than two chronic conditions.

For patients multimorbidity becomes a real problem mainly if it limits daily functioning and if it leads to a loss of vitality. In such cases, care providers not only have to ensure continuity and cohesion in the generally complex medical and nursing care, but they also have to prevent further loss of functioning and

social participation. In this respect the co-occurrence of medical and psychiatric illnesses need special attention.

Four areas need further development

The committee is of the opinion that the current healthcare provisions are not adequately set up to deal with elderly patients with multimorbidity. In order to bring about integrated care for the elderly, development is required in four areas which currently fall short:

- Timely identification of health risks related to multimorbidity
- The management of an integrated provision of care for home dwelling elderly with multimorbidity
- The provision of diagnostic and therapeutic advice to GP and home care nurses by medical specialists
- The application of scientific knowledge about complex multimorbidity within the clinical setting.

Care pathways for the elderly within a region should be developed

The committee is of the opinion that regional agreements about care pathways for elderly patients with complex multimorbidity, in which these four issues are implemented, are required. These regional agreements should involve all relevant professionals and organisations, as well as the insurers. To support such an initiative and to promote further development of the geriatric service, the committee has made the following four recommendations:

Improve the availability and accessibility of information

It is vitally important that the relevant care providers have easy access to accessible and up-to-date (electronic) patient records. The developments in this area are promising and should be strongly stimulated. Although developments in other areas are moving more slowly, regional care agreements should nevertheless include agreements relating to the content and implementation of the medical information exchange system. The committee believes that both the content-related and technical development of the electronic patient record (EPR) system should therefore be pursued even more vigorously.

Stimulate training on multimorbidity

To be able to set up an integrated and well-coordinated provision of care for elderly patients with multimorbidity, medical and nursing knowledge on the subject is required. This will require extra training and (ongoing medical) education. Cross-disciplinary training modules have been found to be very useful in promoting interdisciplinary cooperation. The committee therefore recommends offering extra training on multimorbidity in an interdisciplinary setting, which is not only open to medical professionals (general practitioners, nursing home doctors, clinical geriatricians, geriatric internists, geriatric psychiatrists, surgeons, neurologists), but also to nurses, nursing specialists, paramedics and psychologists. As well as the subject-specific areas (such as ways to maintain health and promote recovery in elderly people, and medical options for typical old-age conditions), there should also be a focus in this training on care pathway coordination, on the collaboration involved in such a pathway, and on how to support those in the patient's immediate environment (informal caregivers).

Stimulate scientific research

Research into the content and organisation of medical and nursing care for elderly patients with complex multimorbidity is particularly scarce. The committee therefore recommends developing a coordinated research effort which would fill the largest knowledge gaps. The committee endorses the recommendations made in the 2006 advice from the Advisory Council on Health Research (RGO) entitled "Research into medical care for the elderly".

- Stimulate the design of the 'regular' clinical research in a way that permits making inferences on interventions for the elderly.
- Concentrate the research on the following three areas:
 - the medical care of vulnerable elderly patients with multiple problems
 - guidelines for diseases in the elderly
 - healthcare organisation.
- Concentrate the research in cooperative associations between healthcare practitioners and research institutions.

Further to these recommendations and based on the research areas recommended by the RGO, the committee recommends giving extra attention to research into prevention, such as instruments/methods for timely identification of complex multimorbidity, and into ways of supporting informal caregivers. Priority should also be given to research into the efficacy of periodic medication monitoring and

the way in which patients are involved in the choices concerning their medication and other components of their treatment and care. Efforts to strengthen the collaboration between research and the practical setting, for example with the development of academic workplaces and the national programme for elderly care proposed by the Netherlands organisation for health research and development (ZonMw), should also be given full support. Financing for such initiatives should carry the explicit prerequisite that it will only be granted if the initiative is scientifically evaluated by cooperative associations of healthcare practitioners and research institutions.

Ensure that the boundary conditions for the planned geriatric service are met

Setting up the planned regional care pathways and establishing effective coordination will, particularly in the beginning, require extra time and resources. To be able to continue providing the planned geriatric service, additional resources will also be necessary in the longer term. The committee advises the government to stimulate the effort by ensuring that the necessary financial support is provided.

A number of conditions could be associated with this funding, such as the willingness to undertake systematic evaluations of the planned geriatric services.

Searchlight on radiotherapy

Health Council of the Netherlands. Searchlight on radiotherapy. A vision for 2015. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/27. ISBN: 978-90-5549-739-3 (in Dutch)

Burden of disease through cancer

Cancer, after cardiovascular disease, constitutes the second most important cause of death in the Dutch population with over 30 percent of all deaths (40 000 cases per year in 2005). Every year approximately 75 000 people are diagnosed with a *de novo* case of cancer (incidence), the frequency being almost equal in men and women. Moreover, around 400 000 people every year are affected in some way by the disease (prevalence), either by being diagnosed, getting treated, declared cured, or being alive with the disease. It is estimated on the basis of both epidemiological and demographic trends, that this incidence will continue to rise in the coming years, reaching around 95 000 new cases per year in 2015, and with almost 700 000 people having their health affected in some way by cancer.

The role of radiotherapy

The treatment of patients with cancer usually includes surgical intervention, chemotherapy, or radiotherapy. A combination of these three modalities is often applied. Radiotherapy is an important treatment option and may be intended for both cure or palliation; in the latter case the priority lies with preserving and enhancing the quality of the remaining life span. On the basis of international comparative research one may conclude that about half of all new cancer patients will qualify for radiation therapy, as both primary or secondary treatment, and

often in combination with other treatment modalities. In recent years data from the Dutch National Cancer Registry indeed show that in the Netherlands some 45 to 47% of the patients will get radiotherapy at some stage of their disease. For the main indications (tumors of the breast, lung, prostate, and rectum), the proportion of patients that will undergo radiotherapy is even higher (50 to 80%), but for other indications too (such as cancers of stomach, bladder, pancreas and CNS) the application of radiotherapy is on the rise.

Planning the capacity for radiotherapy

Since many years the aim in the Netherlands has been to make the capacity for radiation treatment correspond as best as possible with the estimated growth of the number of new cancer cases in the population. Both epidemiological trends (changes in the incidence) as well as demographic trends (aging of the population) are taken into account. Data from the National Cancer Registry form the basis for this extrapolation. In this way the expected number of new radiation patients, as well as the total number of radiation treatments can be calculated. This in turn becomes the input for calculating the numbers of linear accelerators and radiation bunkers needed, as well as the number of physicians, physicists and support staff. In the past 20 years it has been shown that this planning model achieves reliable outcomes on which to base the planning of radiotherapy infrastructure.

License to practice radiotherapy (certificate of need)

In the Netherlands hospitals that want to practice radiotherapy should obtain a license from the minister of health. The law on specialized medical interventions (WBMV) sums up the criteria (such as volume, minimum quality requirements, and catchment area needed) that centers must comply with to qualify for this license. The minister of health will review his decision to admit new centers against the background of a specific planning vision document (Planningsbesluit) that gives recommendations for the desired degree of concentration and accessibility of new centers needed. At present there are 21 fully operational radiotherapy centers in the Netherlands. According to the Health Council expert committee, this number ensures adequate accessibility for practically all patients today. However, the current planning vision document (that expired in 2005) badly needs updating: its planning horizon should be extended to the year 2015.

Present state of radiotherapy in the Netherlands

Today, the facilities for radiotherapy (number of centers, linear accelerators and staff) in the Netherlands are just sufficient to enable treatment of the actual number of patients. Moreover, the accessibility of the centers is good (>90% of patients are able to reach a nearby center within one hour), and waiting times are relatively short. Before this favorable situation could be achieved, however, a problematic backlog in the capacity and waiting lists for radiotherapy had developed at the end of the nineties, and had to be dealt with. An accelerated policy procedure was put in motion to make up for the arrears and bring the capacity for radiation treatment to the desired level (between 2000 – 2010). This step-up operation could be achieved only with the close cooperation of all parties involved, and by giving top-priority to the realization of new radiation facilities. According to the Health Council expert committee the lesson to be learned from this history is that the planning for expanding the radiotherapy capacity needed in the coming years (at least till 2015) should start timely, and that plans should be carried into effect without delay.

What is needed for 2015?

The professional organization of radiotherapists/oncologists in the Netherlands (NVRO) has recently published new estimates for the future need of radiotherapy facilities (by 2015): actual and future epidemiological and demographic trends, as well as ongoing scientific developments have been taken into account. These estimates show that an increase of about 50% (as compared to 2005) in the capacity of radiotherapy infrastructure (number of linear accelerators, medical and technical staff) is needed in order to be able to satisfy the expected demand for radiotherapy. This means that the number of radiation treatments is expected to grow from 60 000 in 2005 to around 79 000 in 2015, which requires linear accelerator capacity to grow from 100 units in 2005 to 158 units in 2015, accompanied by the necessary increase of medical, technical and supporting staff. In addition, a shift towards more labor-intensive and complex treatments is expected, which in turn requires an increase in multidisciplinary consultation, resulting in extra workload for the radiation oncologists and physicists involved. The Health Council expert committee subscribes to these viewpoints laid down in the calculations and recommendations that underpin the new estimates published by the NVRO.

New developments in radiotherapy

Scientific and technological developments continue to contribute to the quality and effectiveness of radiotherapy. Primary goals in this respect are: to strive for as precise as possible radiation of the target volume (tumor tissue) in order to achieve local tumor control, while at the same time keeping the radiation dose as low as possible to spare surrounding healthy tissue and vulnerable organs and structures. Much attention is given to efforts to avoid and limit any radiation-induced complications in the short and long run. The aim here is to minimize the compromising effects of radiation on the quality of life. These strategies require the use of novel imaging technologies (e.g. CT, PET, MRI), combined with advanced radiation modalities, such as: intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), stereotactic radiation and proton-beam radiation. A general observation is that these new developments may result in a significant increase of treatment quality, but that they also lead to heavier demands on both personnel and equipment, and to possible cost increases. Routine application of effective new techniques however may lag behind if the capacity for radiotherapy is under strain for longer periods of time.

Quality criteria for radiotherapy centers

In the past decades the Netherlands have seen positive developments in the field of radiotherapy: this treatment has become an integral part of a multidisciplinary approach to cancer and forms an important link in the chain of patient care (through close cooperation with regional cancer care organizations). Another trend that results from this is a growing sub-specialization in the fields of oncology and radiotherapy; this development requires a sufficient yearly patient volume to be seen and treated in order to build and maintain the necessary special expertise. Research has shown that there is a direct association between the volume of patients treated and the expertise of the individual physician and the center as a whole; this correlates strongly with the quality and outcome of the care provided. The efforts in the Netherlands to ensure an adequate patient volume have resulted in the establishment and development of relatively large-size radiotherapy centers, that form part of or collaborate with hospitals that feature extensive oncology facilities.

Practically all Dutch radiotherapy centers meet the recommended criteria for minimum volume of a radiotherapy department (following nationally and internationally accepted standards), namely: at least four linear accelerators and a

staff consisting of at least eight FTE doctors and three FTE physicists. This provides the means to treat a yearly volume of at least 2700 cancer patients. Each center should have a catchment area of about 500 000 population to achieve this. Around one-third of the present 21 centers in the Netherlands today has a capacity of six or more linear accelerators. International comparison shows that the Netherlands are in a favorable position with respect to the infrastructure and capacity of its radiotherapy centers, and also that a number of countries have recently initiated policies that closely resemble the Dutch approach (i.c. national planning, minimum criteria for capacity of infrastructure and staff, concentration of radiotherapy in high-volume centers).

Quality assurance policies

Quality assurance and enhancement has always been a crucial focus of attention in radiotherapy. Until now, this concerned mainly the physical-technical and radiation-safety aspects of radiotherapy, but recently more attention has been given to the quality of the actual care itself (treatment outcomes and complication rates), and also to the overall care process. Quality control systems that are now being developed, focus on the quality and strength of the whole chain of care and the separate organizational processes that make it up. An important aspect is the development of radiotherapy-specific performance indicators, that is: aspects of care that can be measured and quantified, and give an indication of its quality, safety and effectiveness. The professional organizations in radiotherapy have recently embarked on the development and application of such performance indicators, in close collaboration with the Dutch central organization for quality assurance (CBO). The Health Council expert committee wants to emphasize the fact that development of a comprehensive quality assurance policy in radiotherapy still has a long way to go, and that the application of performance indicators as a quality assurance instrument should not give rise to unrealistic expectations in the short run.

Future developments in radiotherapy

The Health Council expert committee has tackled the question how to best prepare and implement the expansion of the capacity in radiotherapy that is needed for 2015. After completion of the recent round one is now confronted with several options. Further expansion of the already existing radiotherapy centers is in accordance with the policy of concentration that was established long ago. This could also take the form of starting new satellite centers, originating from already

existing mother-centers. An essential requirement will be that mother-center and satellite together form one center, guided by a uniform medical care and quality assurance policy. Complex treatment planning and preparation can take place in the main center, while the actual radiation treatment is performed at the satellite location. The satellite should have a minimum capacity of two linear accelerator units. A final option is the establishment of additional new radiotherapy centers. This could be a solution especially in regions that today have a tight capacity for radiotherapy or where the accessibility is suboptimal (extended travel times). The Health Council expert committee takes the view that new centers should also comply with the accepted minimum criteria for volume, and should have access to their own catchment area of 500 000 inhabitants.

Should the licensing requirement be lifted?

Radiotherapy in the Netherlands has since decades been regulated on the basis of a statutory licensing system (Specific Medical Procedures Act – WBMV) giving the minister of health the authority to designate centers. The minister has now put to the Health Council the question whether there exist any decisive reasons that would argue against terminating the central regulation of radiotherapy by the government. This issue refers to his intentions to amend the application of the above mentioned act in general, as well as to ongoing changes in the health care system that should lead to more emphasis on market forces and stronger competition between health care providers.

In order to be able to answer this question, the Health Council expert committee has conducted an analysis of the different effects of applying the WBMV Act, and has carefully identified and weighed the potential advantages and disadvantages of terminating the licensing system. In summary, the committee draws the following conclusions:

- 1 Central regulation by the health minister, by applying the WBMV Act, has until today contributed significantly to the positive development of the quality and effectiveness of radiotherapy in the Netherlands.
 - 2 The same holds true for the system used to estimate the future need for treatment capacity, based on epidemiological and demographic data and trends, and for the policy putting emphasis on the concentration of radiotherapy infrastructure in relatively large centers.
 - 3 The quality of radiotherapy benefits strongly from the promotion of centers that meet minimum criteria for volume of infrastructure and medical and technical staff, which is a requirement for providing safe and (cost)effective
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care. Efforts to develop a dedicated comprehensive quality assurance system for radiotherapy have been initiated, but its completion and application will take many more years.

- 4 To deregulate the current oversight (by lifting the statutory licensing requirement and ending the a priori review of new centers) in fact means that there will be a major shift of responsibility for both planning and quality assurance policies, from the central government to the professional organizations and other stakeholders (health inspectorate, health insurance agencies, hospital managers and patient organizations). In order to fulfill this task responsibly these stakeholders should have access to suitable instruments (such as: an accreditation system, and the authority to audit the quality of centers). A crucial requirement is that there should be a priori review of center quality.
- 5 The committee concludes that all things considered, a possible deregulation may create opportunities for radiotherapy to continue to develop positively as to quality and accessibility of care. However, lifting the statutory licensing requirement also carries the risk that to the much-needed coordination between centers at the national and regional level will crumble away, and that the need for concentration and effective use of costly resources will be disregarded. To avoid these risks certain safeguards have to be installed.

On the basis of their careful analysis the expert committee makes the following recommendations regarding the future development of radiotherapy, and the issue of lifting the licensing requirement in a responsible way:

- 1 To ensure that the capacity for radiotherapy is well-tuned to the expected demand, the present system of national and regional planning should be continued, apart from the issue of whether the government should take the primary responsibility for this.
 - 2 A policy focusing on maintaining and enhancing quality, by having the radiotherapy facilities concentrated in a limited number of centers (compliant with minimum requirements for volume and staff), should also be continued.
 - 3 Deregulation (lifting the licensing requirement) can only be implemented in a responsible way after a comprehensive quality assurance system (including accreditation and a priori quality audit of centers) has been put into place. This will require a transitional period of about three to four years, during which the current legislation (licensing system) should stay in force.
 - 4 If it should appear that the above mentioned quality assurance system cannot be implemented successfully, or that abolishing the licensing requirement would have harmful effects on the present day quality of radiotherapy care,
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then continuation of the current legal framework should be the preferred option.

- 5 The committee urges that in the near future efforts should start to carry into effect the plans for increasing the capacity for radiotherapy in the period up to 2015. This initiative should be taken separate from a decision to deregulate.
- 6 In view of the fact that proton-beam radiotherapy for the time being is still in a phase of early development where many research questions remain unanswered (e.g. indications, effectiveness and cost-effectiveness), the committee recommends that, at least for the coming years, the licensing requirement should apply to this facility.

Coiling or clipping?

Health Council of the Netherlands. Coiling or clipping? Treatment of intracranial aneurysms. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/12. ISBN: 978-90-5549-721-8 (in Dutch)

Until recently the preferred treatment option for patients with intracranial aneurysms was a surgical repair intervention, during which the skull was opened and a clip was placed on the bulge in the threatened artery. This so called 'clipping operation' has been shown effective in preventing (recurrent) life threatening ruptures and subarachnoid hemorrhage. However, in the mean time a new treatment modality has been introduced, the so called 'coiling procedure', in which a catheter is inserted via an incision in the groin and pushed up into the aneurysm, where a platinum coil is placed in position. A big advantage of this endovascular approach is the avoidance of open surgery of the cranium. However, not yet every type of aneurysm can be effectively treated in this way.

The introduction and application of coiling has had important consequences for the care of patients with intracranial aneurysms. In this report the treatment outcomes of both clipping and coiling procedures, in terms of safety and efficacy in the short as well as the long run, are analyzed and compared. This shows that coiling of intracranial aneurysms is sufficiently safe and associated with important advantages over a clipping operation. In particular patients with subarachnoid hemorrhage from a ruptured aneurysm, show better functional rehabilitation after endovascular coiling, when compared to clipping. Also recurrent bleeding is more effectively prevented. Patients with an unruptured aneurysm also show better outcomes with coiling, as compared to clipping, especially patients at an advanced age and with a poor clinical status.

Two aspects of the care for patients with cerebral aneurysms are worthy of special attention. First, a number of studies demonstrate that for both clipping and coiling procedures there is a strong positive association between the number of interventions carried out by the treating physician, and the quality of that treatment in terms of complications, mortality and outcome. This volume-outcome relationship exists for the individual physician as well as for the hospital as a whole. The lesson to be learned from this is that it should be strongly recommended that the care of patients with intracranial aneurysms (both clipping and coiling procedures) be concentrated in specialized centers with high patient volumes. A second aspect concerns the expertise required to perform coiling procedures safely. Clipping surgery is customarily performed by the neurosurgeon, in close consultation with the neurologist. A coiling procedure however, requires the collaboration of an endovascular therapist, usually an interventional neuroradiologist. Since clipping and coiling are to be regarded as complementary treatment modalities, and one should aim for a careful choice of the most appropriate option for each individual aneurysm patient, a centre should preferably offer both treatments. This requires the availability of a multidisciplinary and dedicated neurovascular team.

The Health Council recommends that the professional medical groups involved will now proceed to establish national guidelines for the minimum volume per treating physician and per centre, needed to guarantee the quality of the treatment and maintain their expertise. This should be the basis for agreement on the number of centers needed for the future. In the Netherlands there are now 11 hospitals, including all university medical centers, where both clipping surgery and coiling procedures are performed. The introduction of coiling has caused a shift in the choice of treatment, resulting in three times more coiling than clipping. In the international scientific literature a ratio clipping:coiling of 1:5 is now usually found. This ratio varies rather widely among Dutch hospitals, reflecting the availability of infrastructure.

Data registries kept up by general practitioners show that in the Netherlands almost 34 000 people yearly are affected by an initial acute stroke. In particular those patients with subarachnoid hemorrhage (bleeding between the cerebral membrane caused by a ruptured aneurysm) are at risk to die shortly. This concerns about 5% of all stroke patients. In the end about 900 patients with subarachnoid hemorrhages every year will be eligible for treatment (coiling or clipping), aiming to prevent – often fatal – recurrent bleeding. This number has remained constant over the past years.

Apart from volume and infrastructure, further agreement is also needed concerning specialist education and specific skills training enabling physicians to

perform coiling procedures in a safe manner. Finally, there is a need for improved outcome registration of coiling procedures, in order to better monitor their quality and further development in indications.

Transcranial magnetic stimulation in psychiatry and neurology

Health Council of the Netherlands. Transcranial magnetic stimulation in psychiatry and neurology. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/21. ISBN: 978-90-5549-731-7 (in Dutch)

Does Transcranial Magnetic Stimulation have any effect?

Various institutions have recently begun using a new medical technique. It involves placing a magnetic coil (which generates a magnetic field) on a patient's skull. The aim is to use this magnetic field to influence processes in the brain. This technique is known as Transcranial Magnetic Stimulation or TMS.

The technique is used to ameliorate certain psychiatric symptoms. Research is also under way to determine whether it could be used to treat various neurological diseases. TMS is also a useful tool in brain research.

Is it a practical addition to the existing arsenal of interventions? This is the topic of this horizon scanning/early warning report. It was drafted by a Health Council standing committee which specialises in the evaluation of innovative medical treatments.

Promising results in the treatment of depression

A meta-analysis of 30 selected publications revealed that TMS therapy has beneficial effects in the treatment of depression. This impression is confirmed by one methodologically very sound study in particular, which was reported in the most extensive publication in the meta-analysis. There are no indications that the electromagnetic field causes any adverse side effects which might limit the therapeutic usefulness of this technique.

To date, the only evidence of this technique's usefulness involved treatments lasting just a few weeks. Nevertheless, the results obtained with these patients, who had previously failed to respond to medication, were very encouraging. It seems likely that other groups of patients could also benefit from this new intervention, and that a more protracted period of treatment or increased stimulation might produce still greater improvements.

That is promising, because this local intervention represents an entirely new approach to the treatment of depression. Importantly, the body is not exposed to foreign substances which affect the entire system.

Less evidence of benefits with other indications

Some beneficial effects were also identified in a meta-analysis focusing on this technique's use in connection with hallucinations. That work involved the use of TMS as a treatment for auditory hallucinations in schizophrenic patients who 'hear voices'. Here too, the patients in question had previously shown little or no response to medication. Treatment with TMS resulted in significant reductions in these patients' symptoms. However, the studies examined in this connection were both fewer in number and more restricted in scope than in the case of depression.

In addition, TMS is already being used to assist the recovery of patients who have suffered a stroke. As yet, however, few articles have been published on this topic. The limited amount of work published to date reveals only short-term, marginal improvements.

The use of TMS to treat patients with Parkinson's disease has produced some encouraging results. This technology could be useful in identifying the best site for deep brain stimulation. Whether or not TMS has the potential to reduce tremors is still open to question.

TMS might also be indirectly useful in connection with the treatment of anti-social personality disorder, by making these difficult-to-treat patients more amenable to psychotherapy. However, this option requires further investigation.

Efficacy study required

While the application of TMS appears to be relatively inexpensive, nothing is yet known about its actual cost-effectiveness. Efficacy studies should focus, in particular, on the use of TMS to treat patients suffering from depression who are not responding well to medication. This might also usefully be combined with the development of guidelines for medical professionals in the Netherlands. In this context, it would also be useful to study the longer term effects of TMS therapy.

Role redefinition in health care

Health Council of the Netherlands. Role redefinition in health care. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/25. ISBN: 978-90-5549-737-9 (in Dutch)

Developments in the redefinition of professional roles

A great deal is expected from the redefinition of professional roles in the health care sector. The assumption is that re-demarcation between existing professions and the creation of new professional groups – non-doctors who are nevertheless competent to perform certain medical procedures – will raise quality standards and lead to more efficient care. Quality and efficiency improvements are needed if the sector is to continue providing appropriate care as demand rises. However, little is yet known about the scientific validity of these expectations.

The uncertainty surrounding the effects of role redefinition was identified as one of the remaining obstacles to change by the Council for Public Health and Health Care (RVZ) in 2002. The other obstacles identified by the Council were uncertainty regarding patient and professional acceptance of change, and legal and financial constraints.

Since 2002, role redefinition has become increasingly commonplace and research has been conducted into its impact. Furthermore, the Minister of Health, Welfare and Sport has indicated a wish to revise the Individual Health Care Professions Act (BIG Act) to afford nurses with certain qualifications the authority to practise autonomously. This would allow nurse practitioners and physician assistants – two examples of new health professionals – to perform minor medical procedures.

In other words, there have been developments in clinical practice and in political circles since the RVZ reported on this matter. It would therefore be useful to establish at this juncture whether role redefinition does indeed have the anticipated benefits. The Health Council has accordingly reviewed the scientific evidence with a view to establishing what is currently known about the effectiveness of role redefinition and about the matters that the RVZ's 2002 report identified as potential obstacles to change.

New information about quality and efficiency

The limited scientific evidence available from the Netherlands and other countries, supplemented by expert opinion, reveals a complex picture. The quality of care hardly ever appears to be adversely affected by the re-allocation of duties or the introduction of a new category of health care professional. Thus, one of the main preconditions for responsible role redefinition is usually met.

There is some evidence to suggest that the quality of care is improved by role redefinition, but the improvement is attributable mainly to better patient supervision and support. Apparently, nurse practitioners and physician assistants, as well as practice assistants and practice support workers who do some of the work traditionally undertaken by GPs, give more attention to such matters. However, role redefinition does not appear to have a beneficial influence on other quality indicators, such as effects on public health.

This implies that the efficiency benefits currently attainable are slight. At present, role redefinition tends to consist mainly of the creation of new health professionals; the re-assignment of duties is much less prominent and there is no redesign of the care process. Furthermore, doctors do not feel that their burden has been significantly alleviated by the changes made to date. It could be that redesign of the process would ultimately result in more efficient care.

Relatively little scientific evidence is available regarding any of these matters, however. Consequently, there is little empirical support for the assumptions on which policy is based.

New information about patient and professional acceptance, legislation and finance

What is known about the other obstacles identified in the RVZ's 2002 report? Patients who have been treated by non-doctors with clearly defined medical responsibilities are largely positive about their experiences. If left to their own devices, however, they are inclined to turn to familiar professionals.

Doctors also appear reluctant to change their ways, despite the scope for responsibly delegating certain tasks. The use of protocols could probably increase interprofessional trust. Again, however, it is likely that more could be achieved by process redesign than by task delegation by individual doctors.

Some of the legal constraints that existed in 2002 have been removed by the proposed changes to the BIG Act. Issues nevertheless remain, because not all care practitioners who undertake medical duties are afforded the appropriate legal authority by the amended Act. This could lead to stricter control. If it is decided that further regulation is required, it is important that a middle path is found: while rules are required to ensure quality and safety, freedom of action is also needed to allow adaptation in the care process.

Little more is known about the financial constraints that the RVZ reported in 2002. The introduction of diagnosis-treatment combinations does not appear to create extra problems, because the combinations do not usually specify which care professional should perform a given treatment.

New focus issues

From the analysis set out above, a number of new issues emerge. First and foremost, role redefinition is currently an extension of the existing, familiar care process, whereas it could be achieved in the context of the redesign of that process. It is conceivable that process redesign could also bring about the desired efficiency gains, without detriment to the quality of care, and possibly to its benefit. However, it is also clear that little is yet known about the likely impact of such changes. Long-term research could help to address this situation.

Contributing to prevention

Screening: between hope and hype

Health Council of the Netherlands. Screening: between hope and hype. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/05E. ISBN: 978-90-5549-722-5 (in Dutch and English)

New forms of screening raise new issues

Screening (or population screening) involves the medical examination of individuals who exhibit no health problems with the aim of detecting disease, or an hereditary predisposition to disease, or risk factors that can increase the risk of disease. The government has great expectations of screening, as do caregivers, private individuals, and other groups within the healthcare sector. Developments appear to be moving fast: new forms of screening are either being brought on line within the healthcare sector or are being marketed by commercial organisations.

The focus on novel screening techniques is tied in with changes within the healthcare sector itself. It is also in keeping with many people's need for reassurance on matters of personal health. The rapid growth in the range of various health checks and self-testing kits is also in keeping with a health service that is determined by market forces, with an emphasis on freedom of choice and individual responsibility.

These developments involve both opportunities and threats. The opportunities derive from the fact that new forms of screening can help people to live more healthily, and avoid symptoms and consequences of disease. There are also threats, because it is by no means a foregone conclusion that the benefits of screening will always outweigh the ever-present drawbacks. There is a tendency to introduce screening before it has been properly researched.

It was in this regard that the Minister of Health, Welfare and Sport approached the Health Council of the Netherlands for advice. There are three central issues. The Minister wants a clear idea of forthcoming developments in the area of screening over the next few years. He would also like to know whether the existing criteria for responsible screening still form a sound basis for the evaluation of those developments and of how they are dealt with in other countries. Finally, he has asked for an indication of the significance of developments in this area, in terms of the role and responsibility of government.

The range of screening techniques will expand and diversify

What about scientific developments in this area? Firstly, there has been a rapid generation of new knowledge concerning the genetic backgrounds of many diseases. This often involves common diseases such as cardiovascular diseases, diabetes and certain psychological disorders. These 'multifactorial diseases' involve a variety of genes, which together produce a more or less increased risk of developing the disease in question. The same effect may result from these genes' interaction with external factors such as diet, smoking, or exposure to hormones. A second, partly overlapping development involves the use of biomarkers. These are characteristic abnormalities in DNA, RNA and proteins, which are also associated with a risk of disease. Thirdly, imaging techniques are improving all the time. This can sometimes enable certain diseases (such as cancer) to be detected at an early stage. Fourthly, new questionnaires are being developed for purposes such as the detection of psychological disorders. Finally, there are great expectations for the potential benefits to be gained by the combination of various screening techniques.

Despite the great pace of new scientific and technological developments, this is not necessarily reflected by the rate at which worthwhile new screening options become available. While we have only just started to elucidate the genetic background of many common diseases, it is important to note that responsible screening requires more than just the early detection of disease, or the charting of predisposition or risk factors. To start with, there must be a suitable test for discriminating between those who have the characteristics in question and those who do not. Furthermore, early detection only makes sense if it has been established that those involved can derive health gains or other benefits, and that these advantages outweigh the drawbacks.

This does not detract from the fact that the range of screening options is expected to grow over the course of the next five to ten years. Aside from an increase in the screening options for monogenic disorders (in genetically loaded

families, in newborns, and prior to conception), the main area of development is expected to involve new forms of screening for risk factors for common multifactorial disorders. However, it is not simply a question of increased volume. In a parallel development, the range of screening options is also expected to become more diverse. This will include not only new types of classic population screening, but also screening of risk groups in the border area of regular care, and checks and self-testing kits offered via private channels to consumers. A third development that can be cited in this connection is a blurring of the line between collective prevention and individual care.

Responsible screening criteria remain valid

At international level, there is a broad consensus regarding the criteria to be met by responsible screening. The major conditions involve the required degree of usefulness of such screening for participating individuals, its scientific basis, and the voluntary nature of screening. That normative framework stems from ‘Principles of screening for disease’, which was published forty years ago by J.M.G. Wilson and G. Jungner. In the intervening years it has been further developed and modified by various institutions associated with screening, also in response to new scientific developments in the field of genetic and prenatal screening. While some elements are currently the subject of debate, there is no reason to suppose that this normative framework is not entirely ‘future proof’.

Since these criteria were primarily developed for classic, government-backed large-scale population screening, not all of them are automatically applicable to private sector screening. Accordingly, the requirement that screening must target major health service problems is tied to the use of public (or collective) funding. Obviously, it does not always apply to private screening that is paid for directly by the individuals in question. However, the core of the normative framework: the principle that the provision of screening can only be justified if it has been established that the benefits to the participants outweigh the ever-present drawbacks, applies regardless of whether this is being provided through public or private channels. That principle requires continual, active confirmation.

The government must ensure the availability of screening worthwhile to all

In this area, the government’s duty is twofold. On the one hand, it must ensure that worthwhile screening is available and accessible to everyone. On the other hand, it must protect people from the risks inherent in unsound screening.

The government fulfils the former duty by itself making certain types of screening available. In this connection, it operates mainly via the National Screening Programme and the screening part of larger programme for child healthcare. Which types of screening are eligible for inclusion in those programmes and which are not? In any event, the government clearly must not provide screening that is scientifically unsound, or which in any other respect fails to meet the conditions of responsible screening. Conversely, it is not the case that the government should be expected to provide any and all types of screening that do meet those conditions.

There are good grounds for limiting the range of screening variants that are funded from public or collective resources to those that are capable of generating actual health gains. Thus, screening where this is not the case should be excluded as a matter of principle. One exception is screening (not aimed at generating health gains) in the context of reproduction, including existing screening for Down's syndrome and other severe foetal abnormalities. Whether this takes place via the National Screening Programme or (as is currently the case) via basic cover health insurance is not a matter of principle.

Beyond that, it is inevitable that there be some sort of priority setting. This involves the same sort of decisions as those associated with the issue of which amenities should be included in (or removed from) basic cover health insurance. There is a consensus that, in that case, the factors of disease burden and cost effectiveness should be examined. However, the applicability of these criteria (also with regard to screening) is a topic for research and debate.

The government's duty of care also requires it to ensure that any screening which is not offered by the government itself but which is (via public health insurance cover) part of the public health service, is qualitatively sound. Furthermore, the government is also required to foster research that can lead to worthwhile new screening options, whether or not these are to be incorporated into the range of screening provided by the government.

The current level of protection against the risks of unsound screening is inadequate

Screening almost always has some drawbacks. It is not merely that false-positive test results ('false alarms') and over-diagnosis (an anomaly is identified, but it is not one that without screening would have led to symptoms of disease) are associated with unnecessary feelings of fear and uncertainty, they can also result in damage to health from high-risk follow-up tests or therapeutic interventions. False-negative results may lead to unfounded reassurance.

Accordingly, the Population Screening Act (WBO) was introduced to protect the public against risks of this kind. The WBO dictates that some types of screening that are considered to involve a significant degree of risk must first be subjected to independent quality testing. In this connection a check is made to see whether provision and implementation are in keeping with the above-mentioned conditions for responsible screening. The screening in question can only be performed once the Minister has granted a permit. The use of self-testing kits for materials produced by the body is, to some extent, governed by different legislation based on a European Directive for in-vitro diagnostic medical devices (IVD Directive).

In addition to a debate about whether the WBO meets current needs, there are problems with compliance. The fact that certain forms of screening (such as total-body scans and prostate cancer screening) are prohibited in the Netherlands, even though their use is permitted elsewhere, is seen by many people as unwanted state intervention. Nevertheless, evidence gathered both in this country and elsewhere clearly underlines the WBO's importance, as an indispensable instrument of protection.

The WBO's biggest problem is that the scope of the protection it offers is determined by the rigid and somewhat arbitrary demarcations imposed by the permit requirement. All other types of screening require no assessment whatsoever. There is another way, however, in which the protective effect of the IVD Directive is found wanting. It cannot effectively prevent the marketing of risky DIY test kits that have not been subjected to adequate quality reviews. Furthermore, the range of self-testing kits that are marketed from outside Europe, via the Internet, is largely beyond the reach of EU legislation.

Finally it is worth considering that, even if people pay for the initial test themselves, unsound screening can have adverse repercussions for the collectively supported health service system. This derives from the fact that a (false-)positive result can give rise to a chain of events that imposes an unnecessary burden on caregivers and resources.

The added value of an active approach

How can the government meet its responsibility in such a way that it covers the entire dynamic arena of publicly and privately available screening and self-testing kits?

Organise continually proactive intervention spanning all areas of screening

It appears that there are better ways of doing this than by simply imposing addition regulations. One such approach would involve continual proactive intervention spanning all areas of screening. The goal would be to identify opportunities for the development of worthwhile new screening options, enhancing the quality of existing options, and enabling people to make well considered choices by equipping them with the requisite knowledge. This will only succeed if the task of active intervention were to be assigned to an independent and authoritative central institution capable of conducting such dealings with the necessary degree of transparency.

Develop a quality mark for responsible screening

Not only would the creation of a 'quality mark' enable people to sort the wheat from the chaff, it would also discourage the provision of unsound screening. A basic variant of this would involve the use of on-line reviews of various types of screening which would be available to the public. A quality mark for screening providers will first have to be devised, however, if this alternative to further regulation is to successfully drive quality improvements in this area. The success or failure of any such quality mark system is largely dependent on the authority of the institution behind it, and upon support from the various parties involved.

Link the quality mark to standards of professional conduct

Wherever possible, use can be made of existing professional guidelines and standards in the area of screening. Conversely, a forceful boost to the development of such quality documents can be linked to the quality mark and to the reviews upon which it is based. Professionals should neither offer nor perform any type of screening that has not been granted a quality mark. This requires the existence of a close relationship between the quality mark and the professional standard. While this cannot be imposed from above, it can grow of its own accord.

Transform the WBO into a flexible safety net

If the categories for which a permit is mandatory were no longer set out in the law itself (but instead in an Order in Council) this would facilitate a more flexi-

ble use of the WBO. The quality mark system would require a more prudent application of the permit requirement. Only where the admission of screening involves a substantial risk (either for the participants or for the health service system) that could not be adequately or fully alleviated by means of the quality mark, would there be a need to introduce a mandatory permit for that form of screening. If used in this way, the permit requirement would operate as an effective 'safety net' for the quality mark system. In advance of such a development, it would seem wise not to make radical changes to the current scope of the permit requirement. Yet it would also be useful to enable the permit requirement to be applied where necessary to prevent the health service system from becoming overloaded by unsound types of screening.

Ensure central control

That continually proactive intervention spanning all areas of screening can best be entrusted to an independent and authoritative institution (a 'Standing Committee on Screening'), which would be charged with:

- Implementing systematic scientific assessments of newly developed screening options, at international level wherever possible;
- Promoting research into worthwhile screening and encouraging population screening trials;
- Contributing to critical reflections on the normative framework itself, and on its further development;
- Advising on the incorporation (or removal) of screening from the range of such services offered by the government or via basic cover health insurance;
- Control over the information and quality mark system;
- Encouraging the development of professional guidelines and standards;
- Pointing out any sticking points that impact the government's duty of protection and giving advice on the scope of the WBO permit requirement;
- Assessment of WBO permit requests.

In addition to independent expertise in all relevant areas, the implementation of these duties requires focused funding and the broadest possible support. In view of its duties in this regard, the government can be expected to make substantial financial commitments. Other parties (insurers, scientific associations) should also be called to account with respect to their own responsibilities in this matter. Additional efforts are required to work out the precise details of embedding and design.

Vaccination against cervical cancer

Health Council of the Netherlands. Vaccination against cervical cancer. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/08E. ISBN: 978-90-5549-711-9 (in Dutch and English)

New vaccine can help to prevent cervical cancer

The Netherlands has had a successful cervical cancer screening programme for several decades. Women between the ages of thirty and sixty are checked for the disease or its precursors, with a view to providing treatment as early as possible in appropriate cases. Recently, however, vaccines have come onto the market, which can be used to prevent cervical cancer – one of the more common forms of cancer in women.

It has been known for some time that persistent infection by human papilloma virus (HPV) is responsible for cervical cancer. HPV is transmitted by sexual contact; most women acquire HPV infections, most of them without any untoward consequences. However, a small percentage of women who become infected go on to develop pre-cancerous conditions and in a small proportion of these women, the pre-cancerous conditions lead to cervical cancer. The vaccines now available prevent the development of the precursors of cervical cancer, and thus are likely to prevent the cancer itself. The use of such vaccines would therefore enable primary prevention, to complement the existing early detection and early treatment activities.

Vaccines require careful assessment before they can be included in the National Immunisation Programme

Now that vaccination against HPV is possible, it is necessary to consider whether such vaccination should be included in the National Immunisation Programme (NIP). The NIP is the vehicle for the provision of large-scale public vaccination in the Netherlands. If inclusion in the programme is considered appropriate, it is also necessary to decide which population groups should undergo vaccination. The Minister of Health, Welfare and Sport accordingly asked the Health Council to address these questions.

New forms of vaccination are not included lightly in the National Immunisation Programme. Inclusion in the NIP implies administration to large numbers of healthy people, which is justifiable only where there is convincing scientific evidence that the vaccination is both effective and safe. Various other criteria must also be met before a vaccination can be added to the NIP list. However, it is important to recognise that absolute satisfaction of any individual criterion is not possible: almost no vaccine is totally effective or entirely without adverse events.

It is not possible to say definitively whether a new form of vaccination should or should not be included in the NIP until it has been carefully assessed against the relevant criteria. Such assessment is required for HPV vaccination just as for any other form of vaccination. Indeed, assessment is all the more important where a new vaccine, such as HPV vaccine, is concerned, since relatively little experience of its use has been gained and little long-term research has been conducted.

The currently available data on efficacy and safety is favourable

The first criterion for admission to the NIP is that the condition addressed by the vaccine must be a serious public health problem. This is self-evidently the case where HPV vaccination is concerned: cervical cancer is a relatively common form of cancer in women between thirty and sixty years old. Despite the existence of an effective screening programme, there are roughly six hundred cases of the disease a year in the Netherlands, leading to the death of between 200 and 250 women.

Whether HPV vaccination satisfies the second criterion – that the vaccination should be an effective means of preventing the relevant disease – is harder to say. The vaccines have been developed only recently and, because the interval between HPV infection and the development of cervical cancer averages about twenty years, there are as yet no data to show whether vaccination leads to a fall

in the incidence of cervical cancer. At present, the only information available relates to the vaccine's effectiveness as a means of preventing HPV infection and the precursors of cervical cancer. Nevertheless, it is reasonable to assume that a lower infection rate and a lower incidence of pre-cancerous conditions – phenomena which *are* demonstrably associated with vaccination – will lead to less cervical cancer. The basis for this assumption is the proven correlation between prolonged HPV infection and the development of cancer of the cervix.

Certainty regarding the effectiveness of vaccination as a means of preventing cervical cancer can be obtained only through clinical use of the vaccine and by following up vaccinated girls and women over an extended period. Further research and conscientious monitoring are therefore essential.

Research has shown that vaccination is useful only if a woman has yet to be infected by HPV. It would therefore seem rational to make the vaccine available to girls at an age when most have yet to become sexually active. The Committee regards twelve years old as appropriate in this regard. The question arises, however: if girls are vaccinated at that age, does the vaccine provide lifelong protection against HPV infection? Unfortunately, this question cannot yet be answered with confidence. Here again, long-term research is required to establish whether booster vaccinations are needed in order to provide proper protection.

It is also worth noting that, even if vaccination were fully efficacious, it could not prevent more than 70 per cent of cervical cancer cases in the Netherlands. The reason being that the available vaccines are designed to protect against two particular cancer-triggering HPV types, which together account for 70 per cent of cases of the disease.

With regard to safety, the third assessment criterion, there is currently no reason to suppose that the vaccine has any adverse events that might preclude its inclusion in the NIP. Nevertheless, the possibility cannot be excluded that, if it were administered to large numbers of people, relatively uncommon adverse events might come to light in due course. This underlines the importance of careful monitoring following the introduction of this form of vaccination.

The cost is relatively high

The fourth and fifth assessment criteria relate to the acceptability of the vaccination in its own right and as an element of the vaccination programme as a whole. The Committee sees no problem on either count: if vaccination against HPV were included in the NIP, it would not represent a disproportionate burden on the target group. Nevertheless, the particular nature of this vaccination does warrant consideration. Given that what is at issue is the vaccination of twelve-year-old

girls against a sexually transmitted infection that can lead to cancer, proper education is very important.

Assessment of HPV vaccination against the sixth criterion – that the vaccination should be an efficient means of preventing the target disease – is more difficult. Because the Netherlands already has a successful cervical cancer screening programme, the benefit attainable by HPV vaccination is less than it would be in a country without such a well organized programme. Consequently, the cost-benefit ratio is less favourable in the Netherlands than in most countries. It should be recognised that the inclusion of HPV vaccination in the NIP would not do away with the need for screening, partly because vaccination does not provide universal protection and partly because unvaccinated women would still need screening.

Given that screening will continue to be necessary even if HPV vaccination is provided through the NIP, the cost of operating the combined programme will be quite high, relative to the attainable health benefit. This is apparent from modelling undertaken specifically to support this report. Furthermore, uncertainty exists regarding a number of factors relevant for modelling, such as the long-term efficacy of the vaccine, the possible need for booster vaccinations, and the price of the vaccine. It is only by monitoring prolonged use that the relationship between the cost of vaccination and the benefits will become clear.

Nevertheless, the Committee believes the capital cost apparent at the present time to be justified by the attainable benefits. It is reasonable to suppose that the provision of HPV vaccination to twelve-year-old girls, in combination with screening, will in due time prevent several hundred more cases of cervical cancer a year, and about a hundred deaths.

Hence, the introduction of this vaccination may be regarded as urgently needed – the seventh and final assessment criterion. No other form of vaccination currently under consideration for inclusion in the NIP is capable of having such a marked effect on mortality. Equally urgent is a catch-up programme of vaccination for girls aged thirteen to sixteen at the time that HPV vaccination is introduced. Considerable health benefit could be obtained by vaccinating females in this age range, since most of them will not yet have been infected by the virus.

Where older girls and women are concerned, consideration should be given to funding vaccination through the Reimbursement System for Pharmaceutical Products (Geneesmiddelenvergoedingssysteem). This would imply communally-funded vaccination outside the context of the NIP.

Inclusion in the NIP requires flanking policy

Assessment against the seven criteria suggests that the admission of HPV vaccination to the NIP would be justified. A particularly attractive feature of such a move is that a certain amount of cervical cancer could be prevented altogether, rather than merely caught early and treated. The Committee accordingly recommends the introduction of HPV vaccination for twelve-year-old girls through the NIP. The Committee further recommends that girls aged thirteen to sixteen at the time that HPV vaccination is introduced be vaccinated in the context of a catch-up programme. Finally, it is also recommended that consideration should be given to asking the Health Care Insurance Board to look at the possibility of funding the vaccination of girls and women aged seventeen or older through the Reimbursement System for Pharmaceutical Products.

The Committee qualifies its recommendations by emphasising that the introduction of HPV vaccination to the NIP should be accompanied by establishment of an ongoing programme for studying and monitoring the effectiveness and safety of this form of vaccination and the longevity of the protection afforded. Other relevant factors, such as public acceptance and the effectiveness of the accompanying education activities (which are very important in this case), require careful evaluation as well. Such steps are necessary in order to obtain the knowledge that is currently lacking, and to ensure that the vaccination programme remains effective and safe.

Following the introduction of HPV vaccination, participation in the cervical cancer screening programme will continue to be very important, even for vaccinated women. It is vital that this message is effectively communicated to the public.

Fetal therapy

Health Council of the Netherlands. Fetal therapy. Update on the current level of knowledge. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/10. ISBN: 978-90-5549-708-9 (in Dutch)

The use of ultrasound scans during pregnancy can detect numerous fetal abnormalities. Some fetal diseases can even be treated before birth. The Health Council published an advisory report on these developments in 1990. This horizon scanning/early warning report gives an update on the current level of knowledge in the Netherlands and beyond. It aims to contribute to the debate on how to safeguard high quality care in the field of fetal therapy in the future.

The most commonly performed invasive fetal treatments are intra-uterine blood transfusion for severe fetal anaemia and the fetoscopic laser coagulation of blood vessels in the placenta of twins with twin-to-twin transfusion syndrome. The number of such procedures carried out in the Netherlands each year are 100 and 45 respectively.

Non-invasive treatment of the fetus by the administration of medications to the mother can be used for conditions such as cardiac arrhythmias, thyroid abnormalities and the production of anti-platelet antibodies. Each of these disorders involves five to ten pregnancies per year. Each year, a few fetuses are treated by using a large-gauge hypodermic needle to insert a shunt (drainage tube) into their thoracic cavity or bladder. Open fetal surgery, in which the mother's abdomen and uterus are opened and then closed-up again once the operation on the fetus is complete, is not carried out in the Netherlands.

Those fetal treatments which are carried out in the Netherlands are either non-invasive or only marginally so. Such treatments pose only a very slight risk to the pregnant mothers themselves. The decision to proceed with fetal treatment

is usually only taken in cases where delaying treatment until after birth is virtually certain to lead to an adverse outcome. Furthermore, most of the children who successfully undergo fetal treatments in the Netherlands have a good chance of being completely healthy. One promising new application is the pre-natal treatment of rare metabolic diseases. This involves keeping pregnant mothers on a special diet or giving them food supplements.

Research is currently being conducted abroad into treating fetuses for diaphragmatic hernias, spina bifida and heart valve stenosis. However, the results of this work will not be available for another three to five years. Should these studies produce favourable results, then the Netherlands will also experience increasing demand for these procedures. Stem-cell therapy and gene therapy are still in the laboratory stages, but it seems sensible to assume that these techniques too will eventually be applied to the treatment of human fetuses.

Given the complexity of fetal therapy (and of invasive fetal therapy) and the small numbers involved, the preconditions for such treatment would be concentration in a small number of centres, complete and transparent reporting, sound scientific research, and cooperation at national and international level. Any proper assessment of the pros and cons of fetal therapy requires that the children receiving treatment be monitored for many years and that they be tested from time to time as they grow up.

Contributing to healthy nutrition

Towards an optimal use of folic acid

Health Council of the Netherlands. Towards an optimal use of folic acid. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/02E. ISBN: 978-90-5549-714-0 (in Dutch and English)

Background to this advice

Regulations and research undergo rapid development

European legislation and research in the field of vitamins, minerals and trace elements (known as micronutrients) undergo rapid development. For this reason, the Minister of Health, Welfare and Sport has asked the Health Council of the Netherlands to reconsider its policy on micronutrients. The aim of the new policy is to ensure that as many people as possible consume adequate quantities of micronutrients while, at the same time, minimising the risk that people exceed the safe upper level of intake.

This advisory report on folic acid is the first in a series of four advisory reports on micronutrients. The other reports will deal with vitamin D, iodine and vitamin A.

Folate is essential for the human body

Folate is a B-vitamin that occurs naturally in food. The synthetic form of folate added to fortified foods and supplements is folic acid. Folate is important for growth and health. Folate deficiency can cause anaemia. Taking additional folic acid around the time of conception lowers the risk of having a child with a neural tube defect.

How can folate intake be improved?

The use of a periconceptual folic acid supplement can be improved

Since 1996 there has been a rise in the number of women who, with the desire to become pregnant, take an additional 400 micrograms per day of folic acid from at least four weeks before conception until eight weeks after. Over the past 10 years there has also been a reduction in the number of foetuses with neural tube defects. Nevertheless, the percentage of women who take the recommended additional folic acid around the time of conception remains too low to achieve the full potential health benefits in this area.

At least three-quarters of women with a non-Dutch background or those with a lower level of education and about half of higher educated women with a Dutch background do not take any periconceptual folic acid supplement, or start too late. Therefore, there is clearly room for further improvement in periconceptual folic acid intake.

Folate intake in the Dutch population does not appear to be optimal

Research into food consumption suggests that the folate intake in about half of all Dutch adults is too low. However, the limited biochemical research available into folate status reveals less dramatic figures: the folate status may be suboptimal in 8 to 25 percent of adults and elderly. The status of children up to 19 years of age has only been examined in one study and seems to be good.

What is the best way to improve folate intake?

The suboptimal folate intake is no reason to change the current policy

The committee believes that supplementation or fortification should yield a clinical benefit. As it remains unclear whether the suboptimal folate status amongst Dutch adults actually causes health problems, there is no reason to improve folate intake in the general population through food fortification or through supplementation.

Improve periconceptual folic acid intake through education and preconception care

To reach the ever-changing target group, the committee recommends a structural increase in education on folic acid use from at least four weeks before conception until eight weeks after. The implementation of preconception care is also advised. These actions should be accompanied by an additional long-term investment in education and care for women with a non-Dutch background or those with a low level of education.

In addition, consider fortifying only staple foods with folic acid

It will be a long time before education and preconception care increase the periconceptual use of folic acid supplements, particularly amongst women of non-Dutch origin or those with a low level of education. In addition, these measures will not reach women with unplanned pregnancies (9 to 15 percent of all pregnancies). For this reason, the government could consider fortifying staple foods, such as bread and bread substitutes, with folic acid so that women are ensured a basic level of folic acid intake around the time of conception. Fortification does not, however, provide the full requirement. That is why the use of folic acid supplements around the time of conception remains warranted.

Currently, fortifying specific food products with folic acid is up to the food manufacturers. This is organized through exemption. The committee is, however, of the opinion that the current policy of exemption, which permits addition of 100 micrograms folic acid per 100 kilocalories to food products, should be limited in such a way that children are no longer at risk of ingesting too much folic acid. In addition, there is no guarantee that all women of childbearing age will use these specific products.

Fortification of staple foods can increase the folic acid intake of nearly all women of childbearing age. For example, the folic acid intake of women can be increased by on average 100 micrograms folic acid per day through fortification of bread and bread substitutes with 150 micrograms folic acid per 100 grams flour after preparation. The committee feels that this level of fortification is acceptable, providing fortification of specific food products is discontinued to avoid children ingesting too much folic acid.

Investigate European regulation of this matter more closely

The conditions called for by the committee when changing the current fortification policy, i.e. limiting or banning voluntary fortification, appear to be at odds with the agreement made within the European Union to avoid any obstruction of free trade. This agreement echoes the 2004 decree of the European Court which states that fortified products may only be refused if they form a specific danger to public health. From a public health point of view, the committee recommends a closer investigation of the regulations on this matter.

If nothing changes yet, create greater control over fortification and clearer labeling

Alternatively, the government could increase its control over voluntary fortification of food products through discussions with manufacturers. It is also possible to make the labeling clearer on foods which have been voluntarily fortified with folic acid so that these can be recommended to women of childbearing age through education and preconception care.

Avoid excessive folic acid intake through fortified foods at any rate

The committee emphasises that, when fortifying foods, it is essential to ensure that folic acid intake remains below the safe upper level of intake. Children are at greatest risk of exceeding the safe upper level when foods are fortified. There is very little research into the potential health risks of folic acid in children. It has also been suggested that in adults very high doses of folic acid may promote the development of cancer.

Patients with benign colorectal tumours should be warned against dietary supplements with folic acid

The committee advises doctors to warn patients with benign colorectal tumours against using dietary supplements containing folic acid. It cannot be ruled out that a high folic acid intake may accelerate the transformation of a benign tumour into a malignant one.

Monitor the potential health effects of the chosen approach

The committee recommends monitoring the effect of the chosen policy on the intake of folate and folic acid, as well as the risk of neural tube defects, the masking of vitamin B₁₂ deficiency, and the incidence of colon cancer, and stroke. Where possible, this monitoring should be carried out using existing registration systems. The committee finds further research essential to determine if, and how folate and folic acid relate to the risk of colon cancer.

Evaluate the dietary reference values for folate

The committee suggests that the dietary reference values for folate should be evaluated, since biochemical data indicate that folate intake in the Dutch population may not be as bad as suggested by food consumption data.

Towards maintaining an optimum iodine intake

Health Council of the Netherlands. Towards maintaining an optimum iodine intake. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/14E. ISBN: 978-90-5549-747-8 (in Dutch and English)

Background of this advisory report

Regulations and research undergo rapid development

European regulations, legislation and research in the field of vitamins, minerals and trace elements, so-called micro-nutrients, undergo rapid development. For this reason, the minister of Health, Welfare and Sport asked the Health Council of the Netherlands for advice on reconsidering its policy in this area.

The aim of the new policy is to ensure that as many people as possible consume adequate quantities of micronutrients while, at the same time, minimising the risk that people exceed the safe upper level of intake. In this advisory report, the specially appointed Committee outlines the requirements for iodine.

Iodine is essential for the body

Iodine is an essential component of thyroid hormones. These hormones are necessary for normal growth and development and to keep metabolism balanced.

Because foods naturally contain little iodine, it may be added to salt

Iodine is a trace element that occurs naturally in food. Because the amount naturally present in the Netherlands is insufficient, iodine may be added to salt.

Baker's salt, used for baking bread and other baked products, contains more iodine (up to 65 milligrams per kilogram of salt) than iodised salt destined for other foods (up to 25 milligrams per kilogram of salt). Roughly 50% of iodine intake is from bread.

Iodine intake is sufficient

As the title of the advisory report already indicates, the amount of iodine consumed by the Dutch population is sufficient. However, there are a number of gaps in the numbers – there is insufficient data on people who only consume self-baked or organic bread, which may contain non-iodised salt or sea salt.

Developments that may lead to lower intake

The determination of maximum levels for voluntary fortification on a European level may lead to lower iodine intake

In the near future, minimum and maximum levels for voluntary fortification will be agreed upon at a European level. If the maximum level of fortification ends up lower than 65 milligrams per kilogram of salt, iodine intake in the Netherlands will decrease, and the risk of iodine deficiency and goitre will increase.

Efforts to decrease salt consumption lead to lower iodine intake

The current level of iodine intake will drop due to the decrease in salt intake. From a public health standpoint, decreasing salt intake is highly desirable. However, it will be associated with a larger risk of iodine deficiency and goitre if iodine intake is not compensated.

Efforts to address these developments

Ensure that the current Dutch level of fortification of baker's salt remains allowed at a European level

In order to safeguard good iodine supply in the Netherlands, it is of vital importance to continue to allow the current level of iodine fortification for baker's salt at a European level. Therefore, a maximum level for salt fortification with iodine of at least 65 milligrams per kilogram should be strived for.

Monitor iodine intake in the Netherlands

Given the efforts to lower salt consumption in the Netherlands, regularly determining iodine intake and status among the Dutch population is important. Fortification policies can be adjusted based on these data. Given the essential role iodine plays in human development, it is important that particular attention is paid to children during their first year of life and to pregnant or breast-feeding women.

Additional research

Investigate the iodine intake of people who only eat self-baked or organic bread

There are insufficient data to determine whether the iodine intake of people who eat self-baked or organic bread is sufficient. This should be examined separately.

Define dietary reference values for iodine

There are no official dietary reference values for iodine intake in the Netherlands. The Committee recommends defining them.

Towards an adequate intake of vitamin D

Health Council of the Netherlands. Towards an adequate intake of vitamin D. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/15E. ISBN: 978-90-5549-746-1 (in Dutch and English)

What is the background to this advisory report?

Regulations and research undergo rapid development

European regulations, legislation and research in the field of vitamins, minerals and trace elements, known as micronutrients, undergo rapid development. It is for this reason that the Minister for Health, Welfare and Sport has asked the Health Council of the Netherlands for advice on reviewing its policy in this area in the light of new scientific developments.

The aim of the new policy is to ensure that as many people as possible consume adequate quantities of micronutrients while, at the same time, minimising the risk that people exceed the safe upper level of intake. In this advisory report, the committee set up to address this issue indicates the requirements for vitamin D.

Vitamin D is essential to the body

Vitamin D can be obtained from food, but strictly speaking it is not a true vitamin. That is because between April and October it can be produced in our skin thanks to the action of sunlight (ultraviolet radiation).

The amount of vitamin D produced in the skin depends not only on exposure to daylight but also on skin colour: less vitamin D is produced in dark skins than

in pale skins. Vitamin D is important for strong bones, along with calcium. Insufficient vitamin D is also associated with muscle weakness and muscle cramps. A severe deficiency leads to weak, painful bones in children and the elderly. An excessively high vitamin D intake causes excessively high blood calcium levels, which gives symptoms of poisoning such as loss of appetite, weakness, fatigue, disorientation and vomiting. If this persists, calcium is deposited around organs such as the kidneys, the urinary tract, blood vessel walls, muscles and tendons.

What are the main scientific developments?

The amount of vitamin D in the body can be measured by means of an indicator: blood serum calcidiol levels. In 2000 the Health Council established dietary reference values for vitamin D on the basis of a serum calcidiol level of 30 nmol per litre. In this advisory report the committee sets a higher target figure (at least 50 nmol per litre of blood) for women aged 50 and over and men aged 70 and over.

This conclusion is based on recent research into the effects of vitamin D and calcium on bone quality, the risk of fracture and the risk of falling in the elderly. The effects are the largest among post-menopausal women who are institutionalized. As bone loss accelerates around the menopause, the committee assumes that the higher target is appropriate for women aged 50 and over.

A good vitamin D supply is known to be important for bone quality and has recently been linked to a lower risk of many other conditions as well, such as cardiovascular disease, auto-immune diseases, infectious diseases and type 2 diabetes. However, the committee finds that the evidence for these effects is not yet strong enough to allow it to issue recommendations.

What is the position with regard to vitamin D supply?

Vitamin D deficiency occurs in all sections of the Dutch population

Inadequate vitamin D status is observed in all sections of the Dutch population. The proportion is higher at the end of winter than at the end of summer (table 1). The figures for pregnant women are probably also applicable for women who are breastfeeding. Vitamin D intake is also too low among children aged up to four who are not receiving follow-on milk or a vitamin D supplement (about four per cent of children aged one year and twelve per cent of children aged eighteen months).

Table 1 The occurrence of vitamin D deficiency among the Dutch population.

Population group	Serum calcidiol criterion	Percentage throughout the year ^a	Percentage in summer	Percentage in winter
Newborn infants with light skin	< 30 nmol/l	15		
Newborn infants with dark skin	< 30 nmol/l	65		
Children with light skin	< 30 nmol/l	5	0	
Children with dark skin	< 30 nmol/l	15-30		40
Children on a macrobiotic diet	< 30 nmol/l		10	80
Adults with light skin	< 30 nmol/l	5-10		
Adults with dark skin	< 30 nmol/l	15-60		
Pregnant women with light skin	< 30 nmol/l	5-10		
Pregnant women with dark skin	< 30 nmol/l	55-65		
Elderly people living independently	< 50 nmol/l	50	35	50
Residents of care homes	< 50 nmol/l	0-85		

^a The percentages are rounded to the nearest 5, as different cut-off points were used in the various studies.

What is the best way of improving vitamin D supply?

Provide more information about the importance of vitamin D, and make the message consistent

The committee feels that the current information is not altogether clear. It is important that the various official bodies involved in the provision of information about boosting vitamin D intake by means of supplement or diet should give the same advice.

A positive exception is the provision of advice on supplements for children aged up to four, where new actions have been taken to increase the use of supplements. Pre-conception care units and infant welfare centres could be involved in recommending additional vitamin D intake during pregnancy and while women are breastfeeding.

Underline the importance of spending at least a quarter of an hour a day out of doors

The committee recommends that people should spend at least a quarter of an hour a day out of doors to help vitamin D production in the body, while taking care to avoid sunburn. The committee feels that exposing at least the head and hands should not be emphasized in the information, because it is actually brief exposure of larger parts of the body, such as the arms and legs, that boosts vitamin D production. But this exposure only generates vitamin D between April and

October. During the winter, people rely on the physical reserve of vitamin D they have built up over the summer in combination with dietary vitamin D.

Also stress the importance of supplementing intake through diet

A healthy diet should provide enough vitamin D (and calcium) for people aged between four and 50 (women) or 70 (men) with light skin who spend enough time outdoors. All other groups need additional vitamin D from supplements.

People who do not take supplements would benefit from eating foodstuffs fortified with vitamin D, but very few such foodstuffs are currently available. And even if there were enough products on the market, their consumption would not provide all the additional vitamin D needed.

The information should contain clear recommendations for additional vitamin D

The committee believes that the currently recommended additional vitamin D levels for certain groups are too low. It advises the following targets:

- an additional 10 micrograms of vitamin D a day for:
 - children aged up to four* ;
 - people aged between four and 50 (women) or 70 (men) who have dark skin, who do not spend enough time outdoors;
 - women aged up to 50 who wear a veil;
 - women who are pregnant or are breastfeeding;
 - people aged over 50 (women) or 70 (men) who have light skin and who spend enough time outdoors.
- an additional 20 micrograms of vitamin D a day for:
 - people who have osteoporosis, who live in a care home or nursing home, people aged over 50 (women) or 70 (men) who have dark skin or who do not spend enough time outdoors, and women aged over 50 who wear a veil.

The committee assumes hereby that calcium intake is adequate.**

* This advice does not apply to children consuming more than half a litre of infant formula or follow-on formula a day.

** 'Adequate' in the sense that it is at the level of the dietary reference value.

Importance of preventing excessively high vitamin D intake from supplements and/or dietary sources

The committee emphasises that it is essential for vitamin D intake to remain below the safe upper intake limit when people are taking supplements and/or eating fortified foodstuffs. Dietary supplements that contain more than the quantities of vitamin D given above in a daily ration must therefore be taken with caution. Children are at the greatest risk of exceeding this limit. The committee advises addressing this issue by registering the composition of fortified foodstuffs: at the moment it is not known precisely which foodstuffs are fortified with vitamin D and how much they contain. This information is however available for supplements.

It is also important that dietary vitamin D intake and the vitamin D status of the Dutch population as a whole and of high-risk groups in particular are monitored. Policy may be adjusted in the light of the results.

Measures can also be taken at European level

The committee thinks that vitamin D should continue to be added to margarine, low-fat margarine, and products used in baking and frying. It also recommends that the type of foodstuffs to which vitamin D can be added in Europe should be restricted to milk, milk substitutes and oil, rather than allowing it to be added to any product without restriction as is the case at present. The advantage of these products is that they are consumed in large quantities by high-risk groups. The advisory report contains proposed fortification levels for these products, which do not put children or adults at risk of excessively high intake when they are consumed in combination with supplements.

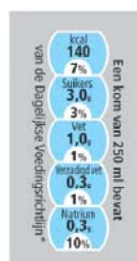
Healthy nutrition: a closer look at logos

Health Council of the Netherlands. Healthy nutrition: a closer look at logos. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/22E. ISBN: 978-90-5549-734-8 (in Dutch and English)

Food companies have various ways of indicating that certain products are good for one's health. Logos for this were introduced in the Netherlands several years ago.



The Choices stamp is an initiative by Unilever, Friesland Foods and Campina. More than one hundred companies now participate in this initiative and many of these companies have products that carry the Choices stamp. The Healthy Choice Clover is an initiative by Albert Heijn. Only the Own-Brand products of this supermarket chain are eligible for the Healthy Choice Clover. Each of these logos is awarded according to their own set of criteria.



Another way of informing people about the nutritional value of food products is by listing the levels of nutrients (nutritional information) on the product packaging. Recently a new format has been introduced to present this information front-of-pack, the so-called GDA system. This system was developed by the European umbrella organisation of the food industry.

The use of logos provides opportunities for improving dietary habits and public health. Whether this will actually occur, depends on three aspects. Are the logos assigned according to sound criteria? Do the consumers use this information correctly when choosing products? Do the logos stimulate manufacturers to improve their range of products? In this advisory report, the two existing Dutch logos will be compared on these points based on the current state of scientific knowledge.

This advisory report also contains an evaluation of the GDA system. This system differs fundamentally from the logos, because nutritional information may be listed on every product and still requires interpretation by the consumers, whilst the logos create the direct message that the product can contribute to a healthy eating pattern, because they are only featured on products that meet the criteria for that logo.

The logo criteria do not sufficiently tie in to the food education

In the Netherlands, the general public education on healthy eating is organised by the Netherlands Nutrition Centre. This is based on the Guidelines for a healthy diet 2006 of the Health Council. The committee is of the opinion that the message communicated by the logos should be consistent with this general food education. Therefore, the committee has compared the criteria for awarding these logos with the evaluation of the health value of food products by the Netherlands Nutrition Centre.

The food education by the Netherlands Nutrition Centre is based on assigning all food products into three categories: 'preferable', 'in moderation' and 'occasionally'; the criteria on which these three categories are based have been described in the Food-Based Dietary Guidelines report. For example, wholemeal bread is put in the category 'preferable', brown bread in the category 'in moderation' and white bread in the category 'occasionally'. As the current logos divide food products into two instead of three categories (products either have the logo or they don't), the committee is of the opinion that the criteria for awarding the logos should be consistent with the 'preferable' category used by the Netherlands Nutrition Centre. Currently, certain 'in moderation' products and even some products that should only be eaten occasionally can be awarded a logo. Based on this starting point, the committee has concluded that the current criteria for awarding the logos must be tightened.

For the Choices stamp, especially the criteria for dietary fibre, the criteria for the saturated fat and added sugar levels of dairy products and the criteria for the calorie content of soups, sauces, snacks and biscuits should be tightened. In the case of the criteria for the Choices stamp, the existing range of products forms

the most important starting point* and not – as for food education – current eating habits in the Netherlands and the desired improvements. This is probably the most important cause of the discrepancies.

In assigning the Healthy Choice Clover, the main problems are the criteria for sodium (table salt), trans fats and ready-to-eat meal products and the lack of criteria for the calorie content of soups and sauces.

The GDA system does not sufficiently tie in to the Dutch Guidelines for a healthy diet 2006

The GDA system provides information about the levels of one or more nutritional factors in a portion of the product. Currently, a manufacturer wishing to display the GDA system on the packaging of a food product has three options: presentation of the calorie content only, presentation of the amount of calories, total fat, saturated fat, total sugar and sodium, or presentation of these five levels plus the fibre content.

The committee is of the opinion that the GDA-system should contain the nutritional factors which, according to the Guidelines for a healthy diet 2006, are of importance for evaluating the health benefits of foods. The total fat content and total sugar content are important for health, because fats and sugars contain calories. However, the GDA system already states the amount of calories in a portion of the food product. People wishing to reduce the number of calories that they consume should, according to the Guidelines for a healthy diet 2006, focus especially on unhealthy fats (saturated and trans fat), added sugar and sugar-rich drinks. The committee recommends for the GDA system to include the following six nutritional factors as a standard: calories, saturated fat, trans fat, free sugars, sodium and fibre. Of these six, dietary fibre is the only one of which consumption should be promoted. The consumption of saturated fat, trans fat, free sugars and sodium should be limited. This also applies to calories for people who are overweight.

The committee endorses the reference values used to calculate the GDA percentages for calories, saturated fat and sodium. The committee urges that the ref-

* The criteria for the Choices stamp are aimed at being attainable for approximately 20 percent of the basic food products and approximately 10 percent of the non-basic food products. The basic food products are vegetables, fruit, bread, potatoes, pasta, rice, legumes, fish, meat (products), poultry, eggs, meat substitutes, dairy, spreadable fats, cooking fats and drinks. They are essential for the provision of nutrients such as vitamins and minerals, this in contrast to non-basic food product groups such as snacks, biscuits, sweets, sauces and soups intended as a starter or snack.

erence value for dietary fibre be increased to the level of the Netherlands fibre guideline and has proposed reference values for free sugars and trans fat.

Little is currently known about how consumers use the logos and the GDA system

The scarce data available indicates that most consumers know that the logos are linked to health in one or another way. A lack of peer-reviewed research makes it impossible to determine whether consumers' eating habits have become healthier as a result of the logos. This requires more research, for example into potential misconceptions.

In the case of nutritional information, it is left to the consumer to determine how healthy or unhealthy a product is. There are indications that fewer than half of consumers, when asked questions about specific values in the GDA system, are able to answer these questions correctly; however, little is known about the comprehensibility of the entire GDA system. Scientific research has shown that consumers are better able to understand nutritional information and find this information more attractive when traffic light colours are used to indicate whether the values are favourable, neutral or unfavourable.

The committee sees a need for further research into the comprehensibility of the logos and the GDA system and the way in which consumers use this information when making product choices.

A favourable effect on product development is plausible for the logos, but not for the GDA system

It is not clear whether the option of placing a logo on food product packaging will stimulate the industry to improve the composition of their products or to develop healthy products, because there has been no scientific research on this subject. Based on information gathered from hearings with manufacturers and organisations involved, the committee does deem this incentive to be plausible for the logos. The hearings provided no consistent indications of an effect for the GDA system on product development.

A sketch of the ideal situation

According to the committee, the ideal situation would be as follows. In the Netherlands, there would be one logo for the promotion of healthy food choices, which would tie in seamlessly with the general public education on healthy eat-

ing. All products that meet the criteria will carry this logo, so that not only the presence, but also the absence of the logo will provide information about the health benefits of the product. In addition, the nutritional information – which allows consumers to evaluate the health benefits of the product – would be listed on the front of the packaging on all products (irrespective of whether it carries a logo).

A plea for one single logo with two different manifestations

According to the committee, consistency between the logos and the general public education on healthy eating is the main priority in creating clarity for the consumers. As long as there is no convincing evidence that consumers are able to handle logos that indicate whether or not the product is relatively healthy within its own product group, the committee is of the opinion that logos should only be awarded to healthy products.

If the current logos are maintained, in which products are divided into two groups (with and without logo), the committee is of the opinion that only products that are preferable according to general public education on healthy eating should be eligible for the logo. This choice most closely matches that of the Dutch Guidelines for a healthy diet 2006. This means that the logo criteria will have to be substantially tightened and the objection is that a large number of products will lose the logo. This may affect consumer confidence in the logos, is bad for the potential effect on product development and is also unfavourable for the consumer, because there will be less choice within the logo range.

Therefore, the committee urges the development of a logo with two manifestations, in which one form is used for food products that should preferably be eaten, according to the food education and the other form for the products in the ‘eat in moderation’ category. A condition for this system would be that research would have to determine whether such a logo with two manifestations would be sufficiently understandable to the consumer. Application of the logo with two manifestations would allow the range of logo products to be maintained, without this affecting the educational message.

The GDA system requires modification

The committee is of the opinion that the GDA system should contain standard information about the amount of calories, saturated and trans fats, free sugars, sodium and dietary fibre. The committee recommends that a colour code indicates whether levels in the product are favourable, neutral or unfavourable levels.

Without such a colour code the GDA system will not be understood properly. The committee recommends to study how such colour code should be used in order to make the GDA-systeem more comprehensible.

The information about logos and the GDA system to the consumer must be improved

The committee recommends that a new information system will be drawn up for consumers, in which the logos and the GDA system are explained in reference to the general public education on healthy eating. Such a system should also pay attention to the importance of a healthy diet and sufficient physical activity. The system should be accessible to all and should be maintained centrally.

Towards an adequate intake of vitamin A

Health Council of the Netherlands. Towards an adequate intake of vitamin A. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/26. ISBN: 978-90-5549-738-6 (in Dutch)

Background to this advisory report

Regulations and research undergo rapid development

European legislation, regulations and research in the field of vitamins, minerals and trace elements, known as micronutrients, undergo rapid development. That is why the Minister for Health, Welfare and Sport has asked the Health Council of the Netherlands for advice in connection with a review of policy in this area.

The aim of the policy is to ensure that as many people as possible consume adequate quantities of micronutrients, while at the same time, minimising the risk that people exceed the safe upper level of intake. In this advisory report, a specially appointed committee indicates what is necessary in the case of vitamin A.

Vitamin A is essential for the body

Vitamin A is a fat-soluble vitamin that is important for sight at low light levels, for reproduction, the immune system, growth and development. Too much vitamin A can cause problems in the functioning of the liver and, in the case of pregnant women, in foetal development. That is why pregnant women should avoid liver, liver products and supplements containing vitamin A.

There are various sources of vitamin A

Only foodstuffs of animal origin contain vitamin A: liver and liver products contain large amounts. It is also added to margarine, low-fat margarine and products used for baking and frying (except oils), in the same proportions as are naturally found in butter. The body can also produce vitamin A itself from provitamin A carotenoids. The main sources of these provitamins are dark green leafy vegetables and some yellow and orange varieties of fruits and vegetables. Dairy fat and egg yolk also contain these substances.

What are the main scientific developments?

A high intake of beta carotene from supplements increases the risk of lung cancer among certain groups

Experimental research has shown that the use of supplements containing at least 20 milligrams of beta carotene a day increases the risk of lung cancer in smokers and asbestos workers.

A high vitamin A intake may be associated with a greater risk of osteoporosis

Observational research indicates that a high intake of vitamin A from foodstuffs and supplements may be associated with a greater risk of osteoporosis.

What is the situation with regard to vitamin A intake?

It appears that both excessively high and excessively low vitamin A intake occur

Data on vitamin A intake reveals that 20 to 30 per cent of the Dutch population may have an excessively low vitamin A intake. On the other hand, almost 10 per cent of children aged two or three may have an excessively high intake, consuming up to 600 microgram retinol activity equivalents (RAE) too much of vitamin A. This excessively high intake is related mainly to consumption of large amounts of liver, liver products and supplements containing vitamin A. Further research is needed to ascertain whether this poses a real problem.

How can vitamin A intake be improved?

A good, varied diet provides enough vitamin A

A good, varied diet provides enough vitamin A without exposing people to the risk of excessively high intake. The latter point is not true in the case of women who are pregnant or who plan to conceive: the committee is of the opinion that these groups should still be advised to avoid liver, liver products and dietary supplements containing vitamin A during pregnancy in order to reduce the risk of congenital abnormalities in the child.

Smokers should be advised against taking supplements with high doses of beta carotene

Smokers and asbestos workers should be advised (besides the advice to give up smoking) to avoid taking supplements containing 20 milligrams of beta carotene or more a day.

What other aspects need to be investigated?

Research into whether an excessively low intake of vitamin A really causes vitamin A deficiency

The committee recommends that research using stable isotopes be conducted into the vitamin A status of people who do not consume margarine, low-fat margarine or non-oil products used for baking and frying. The results of this research should indicate whether vitamin A intake is really inadequate in these individuals.

Research into whether an excessively high intake of vitamin A among children is really a problem

In order to ascertain whether excessively high vitamin A intake among young children is really a problem, research should be conducted into the link between vitamin A intake and the activity of liver enzymes in the blood, the children's vitamin A status and the extent of vitamin A accumulation in the liver.

Research as to whether an excessively high intake of vitamin A increases the risk of osteoporosis

The committee believes that further research is needed into the indications that high vitamin A intake is associated with lower bone density and a greater risk of bone fracture.

Evaluate the dietary reference values for vitamin A

The dietary reference values and safe upper levels of intake for vitamin A were drawn up in 1989. In this advisory report the committee has moved on from these values, using instead dietary reference values based on those established by the American Institute of Medicine, in which Dutch growth curves have been incorporated. It has also used the safe upper levels of intake established by the EU Scientific Committee on Food.

Contributing to environmental health

Uncertainty factors in risk assessment

Health Council of the Netherlands. Uncertainty factors in risk assessment. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/13. ISBN: 978-90-5549-720-1 (in Dutch and English)

This advisory report is concerned with scientific developments that are important in relation to the use of so-called ‘uncertainty factors’ for the determination of health-based recommended exposure limits and for toxicological risk assessment. Such factors are used to make allowance for differences between laboratory animal species and humans, for inter-personal sensitivity variations and for shortcomings in the research data (chapters 1 and 2).

The report covers various scientific disciplines and methodologies. Toxicological insight into substance kinetics and dynamics is increasing all the time: the absorption, dispersion, metabolism and excretion of substances are increasingly well understood, as are the mechanisms by which substances can be toxic to organisms that are exposed to them. Various molecular analysis techniques, cell culture techniques and computer modelling methods are proving valuable in this context. In more and more cases, such methodologies make it possible to specify the qualitative and quantitative differences between laboratory animals and humans (chapter 3).

Chapter 4 reviews current scientific thinking with regard to appropriate numeric values for the various uncertainty factors. The basic principle advocated is that case-specific values should be assigned where possible, and default values used otherwise.

Epidemiologists are also looking for new ways of enhancing research quality and increasing the evidential value of research data. Important developments include the emergence of validated methods for the estimation of past exposure,

the use of biomarkers (early effects known to serve as predictors of subsequent health deterioration) and statistical analysis techniques for the combination of data from various studies (chapter 5). An uncertainty factor for shortcomings in the data can then become smaller or can even become superfluous.

In parallel with the developments outlined above, probabilistic methodologies are entering increasingly widespread use. The problem with default uncertainty factors is that it is unclear how conservative the assigned values are. This issue can be addressed by combining probability distributions, rather than absolute estimates, and then calculating a health-based recommended exposure limit on the basis of an acceptably low degree of probability that adverse effects will occur. Good communication with regulatory bodies is very important in this context, because such methodologies have yet to gain formal approval (chapter 6).

It is sometimes the case that little is known about the toxicity of a substance. Chapter 7 of the report accordingly outlines a number of methods by which it can sometimes nevertheless be possible to calculate recommended exposure limits (albeit provisional or indicative limits) under such circumstances.

The final chapter of the report (chapter 8) summarises the main recommendations of the committee responsible for the report:

- Allometric scaling factors should be used wherever possible.
- The definition of chemical-specific adjustment factors (CSAFs) is preferable whenever enough is known about the toxic activity of a substance. International cooperation in the definition of CSAFs should be encouraged.
- Understanding of toxic activity can be advanced by the application of new toxicological analysis techniques, such as (Q)SARs and *in vitro* methodologies, as well as modelling techniques, such as physiologically based kinetic modelling.
- At the same time, more widespread use and further development of probabilistic methodologies is desirable. These methodologies promise a major improvement on the 'classic' approach, based on the use of default values for uncertainty factors.
- In recent years, there has been increasing interest in methods for the health-based assessment of substances in the absence of ample toxicity data. It is important to encourage and facilitate initiatives in this field.

Hydrogen-powered road vehicles

Health Council of the Netherlands. Hydrogen-powered road vehicles. Positive and negative health effects of new fuel. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/16. ISBN: 978-90-5549-726-3 (in Dutch)

Hydrogen-powered road vehicles: a vision of the future

Because of the political, social and environmental problems associated with dependency on fossil fuels, there is considerable interest in alternative energy sources. Hydrogen is regarded as a promising option, particularly as a fuel for road vehicles. The Dutch Energy Research Centre (ECN) recently published a vision of the future, in which it suggested that by 2050 more than half of all cars in the Netherlands could be running on hydrogen.

Assuming that the hydrogen is produced from renewable energy sources, migration to hydrogen-powered vehicles would also curb carbon dioxide emissions. In the United States, Japan and Europe, considerable public and private investment is therefore being made with a view to developing the technologies needed to make the creation of a hydrogen-based economy possible within a few decades.

A switch to using hydrogen as the primary energy source for road vehicles would have far-reaching social consequences. As with all technological developments, opportunities would be created, but drawbacks would inevitably be encountered as well. Some of the disadvantages associated with hydrogen are already known, and are to some degree manageable. It is likely, however, that other drawbacks would come to light only once hydrogen-powered cars were actually in use.

With that thought in mind, and in view of the social significance of a possible transition to hydrogen, it was decided that the Health Council should assess the positive and negative effects that hydrogen use could have on public health. It is particularly important to make such an assessment at the present early stage in the development of hydrogen technologies, so that gaps in existing scientific knowledge may be identified and appropriate strategies may be developed for addressing such gaps. This report has been produced by the Health and Environment Surveillance Committee, which has special responsibility for the identification of important correlations between environmental factors and public health.

From production to practical use

Like electricity, hydrogen is an energy carrier; its production therefore requires an energy source. As with electricity again, various sources can be used and production may take place at large centralised plants or small distributed units. The finished product may then be brought to the end user in tanks or by pipeline. A road vehicle would carry a supply of hydrogen in a tank, supplying either a combustion engine or a fuel cell to generate electricity for an electric motor.

Health benefits

First, the use of hydrogen as fuel for motorised road vehicles would lead to less air pollution, and thus to improved public health, particularly in urban areas. The only by-product of hydrogen combustion is water, so emissions of the harmful substances associated with conventional combustion engines, such as carbon dioxide and particulates, would be reduced. Traffic-related air pollution would not be eradicated altogether, however: a significant amount of the particulate material released into the atmosphere consists of tiny fragments of tyre rubber and asphalt, for example.

A further health benefit would derive from the fact that vehicles powered by a combination of hydrogen fuel cell and electric motor would be quieter. A general transition to such vehicles would therefore mean less noise pollution and fewer noise-related sleeping problems. Reduced greenhouse gas emissions would also have an indirect health benefit, since climate change would be attenuated and the related adverse health effects mitigated. However, any such benefit would be dependent on the hydrogen being produced by a 'climate friendly' process: hydrogen is itself merely an energy carrier (like electricity), so the sustainability of its use is determined by the manner of its production.

At the present time, there are two production methods that appear to be both feasible and relatively clean. The first involves the use of natural gas, which would result in modest emissions. The second entails the gasification of coal, coupled with underground storage of the unwanted carbon dioxide produced along with the hydrogen. Unfortunately, carbon dioxide storage techniques are as yet in their infancy. Nevertheless, these two methods are the most viable options pending the longer-term development of more sustainable forms of production based on the use of solar, water or wind energy. Other possibilities include biomass gasification and nuclear energy.

Adverse health effects

How might the use of hydrogen as a vehicle fuel adversely affect public health? First, hydrogen use entails fire and explosion risks. Particular attention should be given to these risks, because hydrogen does not behave in the same way as the fuels we are currently used to; any leakage of hydrogen within an enclosed space is especially dangerous. Second, the release of harmful substances from vehicle fuel cells could have an adverse effect on health. The vehicles of the future may have hydrogen fuel cells to generate power for electric motors. Such fuel cells could be associated with the release of harmful particles into the environment, not only during production and use, but also when the cells are scrapped. Unfortunately, it is not yet possible to say which materials are liable to be the most significant in relation to public health. The Committee nevertheless believes that particular attention should be given to the possible implications of the presence of nanoparticles in hydrogen storage tanks and fuel cells.

Hydrogen use might also adversely affect public health by another – very different – mechanism, namely its effect on the composition of the atmosphere and upper air strata. A switch to hydrogen-fuelled vehicles would lead to hydrogen leaks, to the emission of an uncertain amount of greenhouse gas and to an uncertain reduction in the emission of substances such as nitrogen oxides and carbon monoxide. These developments are liable to have implications for the troposphere and stratosphere, and thus for our climate and the ozone layer, but their precise influence is hard to predict. Modelling suggests that the net impact could be positive or negative, and scientific opinion on the influence of hydrogen remains divided.

The known risks should be manageable to some degree, partly by drawing on experience with the industrial use of hydrogen and experience in the field of waste management and recycling. However, the introduction of hydrogen technology is also likely to be accompanied by currently unforeseen risks. It is there-

fore advisable that any such introduction should be incremental and carefully monitored with a view to picking up the signs of any problems as early as possible.

The need for control

The far-reaching consequences of adopting hydrogen technology necessitate monitoring and control. At present, the focus is mainly on the possible environmental benefits, and relatively little attention is being given to the potential hazards. However, if a transition is to take place, the entire spectrum of effects should be considered, insofar as they may be predicted.

In this context, the government has an important coordinating role to play. The sustainability of the production methods and the way in which an infrastructure is realised will be key issues. Systematic consideration needs to be given not only to the implications for the economy and the local and global environment, but also to the public health effects (which will be influenced by the economic and environmental effects). Public support is vital if a successful transition is to be achieved.

With careful transition management, the consideration of health implications can become an integral part of the processes of developing and introducing hydrogen technology. In this way, any adverse health effects can be identified in good time and appropriate corrections made. Furthermore, such a strategy will enable verification of the anticipated health benefits.

The Committee therefore favours an incremental approach to the adoption of hydrogen technology, in the context of a democratic process. While the outcome of that process cannot be predicted, the Committee is confident that the advocated approach would enable the sensible management of unforeseen hazards, and the optimal exploitation of unforeseen opportunities, involving, for example, more sustainable forms of mobility.

Prudent precaution

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Introduction

Does the disappearance of many animal and plant species threaten ecosystem functioning and human health? Is the cultivation of genetically modified crops a threat to people and the environment? Are people working in the cosmetics industry at risk from nanoparticles? Can variant Creutzfeldt-Jakob's disease be communicated in blood and blood products? Science cannot currently answer these and many other questions. However, the uncertainty that surrounds such issues does not mean that they can be relegated to the bottom of the political and policy agenda. In recent decades, there have been increasingly insistent calls for the precautionary principle to be applied in cases of scientific uncertainty, for the protection of public health and the environment. The European Union has incorporated the principle into its treaty and the environmental movement is constantly asking for the precautionary principle to be used to address potential hazards in our surroundings.

Application of the precautionary principle has, however, been the subject of considerable debate. Critics argue that the precautionary principle is vague and unscientific, promotes arbitrary decision-making and inhibits technological development and progress. The principle is also perceived by some to interfere with the efficient use of scarce resources. It is accordingly suggested that policy based on the principle is more likely to have a negative effect on public health than a positive one. The counterargument is that a precautionary approach is

often the only way of ensuring that modern technology does not cause serious irreversible harm.

Against this background, the President of the Health Council established a committee to carry out a scientific analysis of the precautionary principle and to make appropriate recommendations regarding its application. The committee was also asked to assess the significance of the principle for public health policy in its broadest sense, i.e. including the environmental protection, food safety, occupational health and safety and preventive and curative health care domains.

In this report, the committee explains what it believes the precautionary principle entails, identifies the types of issue to which it can be constructively applied and sets out the relevant considerations. The report concludes with a brief assessment of what can be achieved by application of the precautionary principle, as defined and in the manner proposed by the committee. The intention is that the report should serve primarily to guide policy-makers and politicians when considering application of the precautionary principle in government policy. Nevertheless, the committee hopes that the report will be helpful to everyone that is in some way involved in decision-making within the policy domains listed above.

What the precautionary principle entails

Numerous definitions of the precautionary principle can be found in policy documents, international treaties and other political and legal texts. Perhaps the best-known example is the definition given in the declaration issued at the conclusion of the 1992 United Nations Conference on Environment and Development in Rio de Janeiro (the 'Rio Declaration'):

Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.

More recently, a UNESCO committee defined the principle as follows:

When human activities may lead to morally unacceptable harm that is scientifically plausible but uncertain, actions shall be taken to avoid or diminish that harm.

Recently, the European Environment Agency proposed the following definition:

The precautionary principle provides justification for public policy actions in situations of scientific complexity, uncertainty and ignorance, where there may be a need to act in order to avoid, or reduce,

potentially serious or irreversible threats to health or the environment, using an appropriate level of scientific evidence, and taking into account the likely pros and cons of action and inaction.

The various definitions differ in terms of the extent to which they imply action *must* be taken where uncertainty exists, and in terms of the nature of the action required. Hence, distinction is made between ‘strong’ and ‘weak’ versions of the precautionary principle. Proponents of the principle associate it with efforts to achieve sustainability. Many people take the view that the precautionary principle implies that, in situations characterised by serious uncertainty, more weight should be attached to the potential negative consequences of a human activity than to its potential positive consequences. This outlook is consistent with the ideas put forward by the originally German philosopher Hans Jonas. It also has echoes in the ‘maximin’ rule, which is often closely associated with the precautionary principle. This rule – one of many developed by decision scientists to facilitate decision-making in situations of uncertainty – requires that a course of action should be chosen solely on the basis of the potential negative consequences of the various options (the option likely to have the least serious undesirable effect being preferable). However, this rule is useful only in situations where there is little to be gained and a great deal to be lost. The many other available decision rules all have their own limitations. The committee does not therefore believe that any one rule is universally applicable in situations of great uncertainty.

The committee takes the view that greater weight should not *always* be attached to (potential) negative consequences than to (potential) positive consequences. Thus, the committee does not regard the precautionary principle as a decision rule. Foregoing benefits in order to avoid a particular risk can itself introduce other risks. If, for example, children were no longer vaccinated because of concerns about the possibility of neurological damage resulting from the presence of a mercury-containing preservative in vaccines, the risk of infectious disease would increase. The committee therefore sees no alternative to assessing the various possible courses of action and the associated (potential) positive and negative repercussions on their own merits, and weighing them up against one another in a careful and transparent manner. In this context, the precautionary principle may be regarded as a strategy for dealing with uncertainty in an alert, careful, reasonable and transparent fashion, which takes account of the particular situation. In the committee’s view, applying the principle is by no means identical to banning activities, although this may be the preferable option in some cases.

Issues to which the precautionary principle is applicable

Decision-making is more challenging where the policy issue involved is characterised by ambiguity, uncertainty and/or complexity. Ambiguity exists where divergent values are involved. Distinction can be made between normative and interpretative ambiguity. The former involves differences of opinion as to what is ethically acceptable; the latter involves differences of opinion as to the significance of a given research finding (e.g. whether a given effect may be deemed to constitute 'harm'). Interpretative ambiguity is amplified more than normative ambiguity by the second challenging characteristic: uncertainty. Where the introduction of new technologies or products is concerned, uncertainty may exist regarding the hazard characteristics, the levels of exposure and therefore the nature and extent of the harmful effects that might occur, and the likelihood of their occurrence. Where harm has already occurred, uncertainty may exist regarding the possible cause(s). Sources of uncertainty include the variability of phenomena and lack of knowledge, which may entail anything from a measurement error to complete ignorance. Finally, complexity is an expression of the difficulty of developing a qualitatively and quantitatively clear picture of the consequences of a course of action on the basis of the available information. Complexity exists where there are a large number of possible causal factors and effects, and the relationships between them are unclear.

The three characteristics referred to above are interdependent and hard to distinguish from one another. High levels of complexity and uncertainty increase ambiguity, for example. Nevertheless, in principle, each of the characteristics requires a different approach strategy. Ambiguity is best addressed by means of consultation and debate, with a view to identifying common values, fostering understanding and seeking ways of enabling different groups to implement their own visions in practice. Uncertainty requires a strategy for dealing with the uncertain matters in an alert, careful and reasonable fashion, which takes account of the particular situation – in other words, for application of the precautionary principle. Finally, complexity should be tackled by (multidisciplinary) discourse amongst people with scientific and practical expertise, so that the best possible picture of the issue may be built up on the basis of all the available information.

The precautionary principle, therefore, is appropriate for use in connection with issues that are characterised by a degree of uncertainty sufficient to hamper decision-making. To warrant a precautionary approach, it must also be plausible that negative consequences will occur, or that a causal relationship exists. Plausibility needs to be judged by experts, who may apply standard scientific criteria. In the assessment process, the role of non-experts is to make observations and pose

critical questions in order to test and thus contribute to the quality of the experts' arguments. For their part, the experts should be open to such observations and questions, and candid about the extent of their knowledge. In general terms, an effect or correlation may be considered plausible if at least some recognised experts in the relevant field have concerns. Whether the degree of plausibility is sufficient to justify further action (and if so, what that action should be) is a policy decision that must be made on the merits of the individual case. In that context, consideration should be given to the interests at stake and extent to which the issue is liable to cause public disquiet. Most uncertain issues will also be characterised by a degree of ambiguity and complexity. Under such circumstances, it is advisable to formulate a customised approach that integrates the three specialised strategies.

All the policy domains with which the Health Council is concerned (preventive and curative health care, environmental management, occupational health and safety and food) are characterised by uncertainty. Therefore, the committee takes the view that the precautionary principle can usefully be applied in all these domains.

Developments in dealing with risk

Scientific and technological advances, population growth and globalisation are exposing large parts of the world to all sorts of 'new' risks, which it is increasingly difficult for the individual to fully understand or influence, or for experts and governments to specify and control. In parallel with this trend, thinking on how risk should be dealt with has gradually been changing in recent decades: the technical, natural science-based approach (with the focus on the nature, extent and likelihood of possible consequences and the role of mankind) has been broadened to take account of psychological and sociological factors that contribute to public perceptions of risk (control over the risk characteristics, extent to which exposure is optional, confidence in the authorities, etc). Finally, in line with developments in other fields of public administration, an approach referred to as risk governance was adopted, in which stakeholder groups are involved in the development and implementation of risk management policies, and openness and transparency are key principles. The advantages of such an approach are the input of knowledge, experience and views from a wider range of sources and the formulation of policies that are more likely to command general support. The successful involvement of stakeholders in assessment and decision-making is not easy to achieve, however. Factors such as the increasing availability of reliable and unreliable information via the Internet and the greater assertiveness of private citizens

and interest groups have resulted in metamorphosis of the high-trust society into a low-trust society. The committee therefore wishes to see the development of tools and the training of personnel with a view to enhancing implementation of the risk governance process. Although each party undeniably has a responsibility in this context, the principle of democracy requires that the government has ultimate decision-making authority with regard to public policy or defines the parameters within which other actors may decide matters. Depending on the issue in question, decisions may be made at the local, national or international level.

The governance of policy issues should be realised through an assessment and decision-making process divided into a number of steps, in which communication plays a central role (see figure 1). The process needs to involve the exchange of information, making allowance for people’s expectations, feelings and fears, promoting trust and a willingness to engage in debate about values. Specification of the process becomes more laborious and more challenging as the degree of complexity, uncertainty and ambiguity characterising the issue increases. This is particularly so where the participation of stakeholders is concerned. It is advisable that politicians and policy-makers involve scientists and researchers, as well as representatives of the business community, unions and NGOs, including consumers’ and patients’ groups and animal welfare or environmental lobby groups, in the process of assessment and decision-making on uncertain issues. It can be desirable to extend participation to include representatives of the general public (e.g. through citizens’ panels), especially where an issue is also characterised by ambiguity.

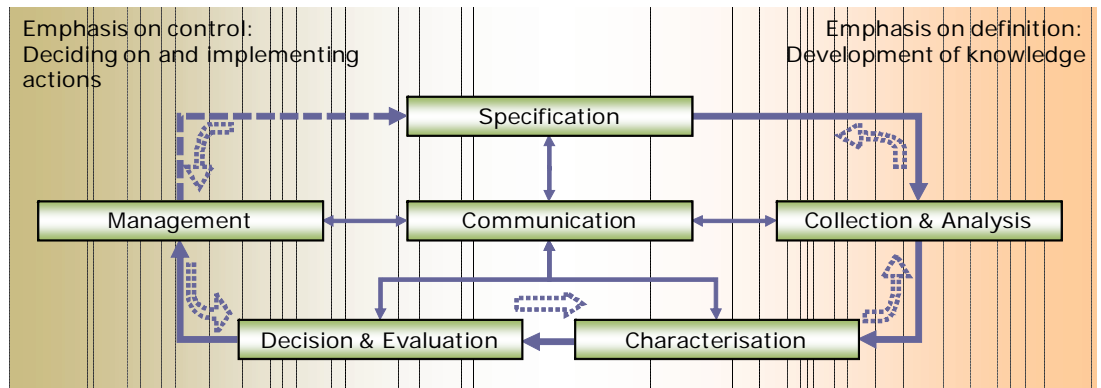


Figure 1 The assessment and decision-making process for policy issues.

Application of the precautionary principle

The Specification stage involves problem definition and demarcation. The decision situation is thoroughly examined and the degree of complexity, uncertainty and ambiguity involved in the relevant issue is established as accurately as possible. If it is concluded that the issue involves substantial uncertainty, application of the precautionary principle is advisable (if necessary in combination with strategies for ambiguity or complexity). Because the precautionary principle entails dealing carefully with uncertainty, precaution is exercised not only in the later stages of the process (Evaluation & Decision-Making and Management), as often suggested, but also in all the preceding stages. The risk-engendering activity is then examined, along with all possible alternatives; in this context, consideration is given to the positive and negative, certain and uncertain consequences of each option. The outcome has implications for the design of all subsequent process steps. It is also necessary to establish who the stakeholders are.

At the Collection and Analysis stage, the relevant data are collected and analysed, and the expectations, feelings, concerns and values of the various stakeholder groups are surveyed. The uncertainty characterising the issue means there is inevitably a risk that an inappropriate course of action is chosen, so it is necessary to build up a picture of the possible consequences (nature, extent, scenarios) of making the wrong decision (insofar as that is possible, given the level of uncertainty). To this end, consideration should be given to the possibility that a course of action subsequently proves to have been excessively cautious, and to the possibility that it proves to have been insufficiently cautious. The (often scarce) evidence for the potential consequences needs to be considered in the same way.

At the Characterisation stage, the available data are summarised and expressed in appropriate units to facilitate decision-making. In the interest of comparability, the consequences of both excessively and insufficiently cautious decisions should ideally be expressed in the same units. However, that is not possible in many cases, because of the dissimilar nature of the consequences. It is also important that assessment is not restricted to readily quantifiable and comparable effects (e.g. effects that can be expressed in monetary terms). If aggregated indicators, such as monetary value or DALYs, are used for comparison, care needs to be taken to ensure that other relevant information, such as the distribution of effects across population groups or between current and future generations, is given proper consideration.

During the Evaluation and Decision-Making stage, policy-makers reach a conclusion as to the course of action that is in society's best interest, in or following consultation with the relevant stakeholders. Arriving at such a decision tends

to be a difficult process, because the various positive and negative implications of the various options are usually difficult to compare. Matters are further complicated by the uncertainty that surrounds (some) of those implications. Decision-makers need to take account not only of the scientific evidence, but also of the importance that people attach to the undesirable potential consequences of both excessive and insufficient caution.

The Management stage involves implementation of the chosen course of action. Because the decision-making process was characterised by uncertainty, the selection of that course of action is in principle provisional. It is important that the consequences are monitored, as a basis for policy review and realignment in the light of new information. Thus, assessment and decision-making guided by the precautionary principle is a dynamic and iterative process throughout.

Practical examples

Several years ago, the European Environment Agency (EEA) considered what lessons could be learned from the previous failure to heed early warnings on twelve policy issues (including asbestos, DES, PCBs and BSE), which had resulted in considerable environmental and health damage. In the preparation of this report, the committee has been guided partly by the EEA's findings. The committee has itself examined three issues, the policy on which is still under development and might yet therefore be improved. The issues in question are the possible toxicity of nanomaterials, the universal fortification of bread and bread products with synthetic folic acid for the prevention of neural tube defects, and intracytoplasmic sperm injection (ICSI) using surgically harvested sperm in cases of male infertility. The committee has demonstrated how these issues should be assessed by outlining the potential implications of decisions based on over-optimistic and over-pessimistic assumptions. Policy development has progressed furthest in relation to ICSI. In the mid-1990s, a moratorium on the use of ICSI with surgically harvested sperm was introduced, because of concerns that the process could result in the birth of children with (epi)genetic defects. Apparently, less weight was attached to the possibility that some people would unnecessarily be denied the opportunity to have children that were genetically their own, than to the possibility of some offspring having serious genetic defects. Because more recent research has suggested that the earlier fears may have been misplaced, the technique has now been cleared for controlled use in a research setting. If the results of the research tend to confirm the safety of the technique, the previously imposed moratorium will serve to illustrate that caution is not without its adverse

consequences. However, provided that a cautious policy results from a careful evaluation process, it cannot legitimately be criticised.

Value of regarding the precautionary principle as a strategy

By calling for the precautionary principle to be regarded as a strategy for dealing with uncertainty in an alert, careful and reasonable fashion, which takes account of the particular situation, the committee has defined a procedural context for the principle. Although application of the principle does not direct decision-making or ease the unavoidable and difficult task of weighing up competing options, it does provide a reference framework within which policy-makers can work. By ensuring that uncertainty is actively taken into account, it serves as a valuable supplement to more traditional policy support tools, such as (classic) risk analysis and cost-utility analysis, and therefore provides a basis for better decisions. Hence, application of the precautionary principle is ultimately beneficial for human health and the environment. It prevents a situation where undue importance is attached to known or probable (and typically short-term) benefits, relative to the associated disadvantages, if these are less certain and likely to manifest themselves only in the long term. Such an approach provides better protection for future generations. While the precautionary principle cannot completely protect society from unpleasant surprises, it can make them less likely. Its application serves to encourage people to consider the potential negative impacts of new technologies right from the start of the development process. It promotes a dynamic and iterative process of policy formulation, monitoring and review, and thus reduces the danger of early warnings being overlooked or lightly discounted and enhances the prospects for early intervention. This in turn leads to the reduction of adverse effects ('learning by restricted error'). Finally, adherence to the principle makes it clear that, in situations characterised by uncertainty, a choice needs to be made between the potential consequences of a policy that subsequently proves to have been very (or unnecessarily) cautious and the potential consequences of one that subsequently proves to have been (too) optimistic. Application of the principle promotes conscious and informed decision-making on such matters. General adoption of the precautionary principle would lead to the establishment of a culture in which uncertainty was consciously addressed, as already happens in the field of radiological protection, guided by the ALARA principle*.

* ALARA (as low as reasonably achievable): a principle intended to guide action to reduce exposure to harmful agents, such as ionising radiation.

The committee believes that, if the precautionary principle is applied in the manner described, the criticisms that have been levelled at it cease to be valid. The proposed methodology does not encourage unduly pessimistic or optimistic assumptions; it utilises the available knowledge to the full without absolute reliance on scientific proof; and it guides technological progress without inhibiting it. The principle is defined in general terms, because that is a requirement for applicability in relation to a wide range of issues; detailed practical specification will be necessary on a case-by-case basis. Finally, the principle is more likely to lead to tailor-made solutions than to arbitrary policy, provided that all stakeholders work together in the context of a careful, government-supervised risk assessment and decision-making process to identify a reasonable way of accommodating the uncertainties associated with the issue in question, while heeding the interests of future generations.

Recommendations

The committee's recommendations may be summarised as follows:

- The precautionary principle should be regarded as a strategy for dealing with uncertainty in an alert, careful, reasonable and transparent fashion, which takes account of the particular situation.
 - The precautionary principle should be applied in connection with issues that are characterised by a substantial degree of uncertainty, i.e. a degree of uncertainty sufficient to hamper decision-making. Where the introduction of new technologies or products is concerned, such uncertainty may relate to the hazard characteristics, the levels of exposure and therefore the nature and extent of the harmful effects that might occur, and the likelihood of their occurrence. Where harm has already occurred, the uncertainty may concern the possibility of a causal relationship with previously introduced products or technologies.
 - The plausibility of a threat or an association should be judged by experts, who should be open to observations and critical questions from non-experts, and candid about what is uncertain. Whether the degree of plausibility is sufficient to justify action (and if so, what that action should be) depends on the interests at stake and the level of public disquiet.
 - Most uncertain issues are also characterised by a degree of ambiguity and complexity. Under such circumstances, it is advisable to formulate a customised approach that integrates the precautionary principle and the specialised strategies for ambiguous and complex issues.
 - In a given case, various possible courses of action should be assessed on their own merits, together with the associated (potential) positive and negative
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repercussions. The various options should be weighed up against one another in a careful and transparent manner.

- Proper consideration must be given to effects that cannot easily be quantified, and to matters such as the distribution of effects across population groups or between current and future generations.
- When choosing a course of action, account must be taken not only of the (sometimes limited) scientific evidence for each potential consequence, but also of the importance that people attach to the undesirable potential consequences of both excessive and insufficient caution.
- Appropriate stakeholder groups should be involved in the assessment and decision-making process associated with risk issues (risk governance). This will lead to the input of knowledge, experience and views from a wider range of sources, greater transparency and the formulation of policies that are more likely to command general support.
- Tools should be developed and personnel trained with a view to enhancing implementation of the challenging risk governance process.
- The outcome of implementation should be monitored as a basis for policy review and realignment in the light of new information, so that assessment and decision-making guided by the precautionary principle is a dynamic and iterative process throughout.
- The precautionary principle should be applied in all health-related policy domains: preventive and curative health care, environmental management, occupational health and safety and food.
- Make it common practice to apply the precautionary principle and create thus a culture, in which it is the norm for uncertainty to be addressed carefully.

Contributing to healthy working conditions

Prevention of work-related airway allergies

Health Council of the Netherlands. Prevention of work-related airway allergies. Recommended occupational exposure limits and periodic screening. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/03E. ISBN: 978-90-5549-710-2 (in Dutch and English)

Allergic respiratory disorders are a significant problem

Occupational allergic disorders are commonly reported illnesses arising from exposure to allergens. An allergic disorder is a significant problem because, if exposure continues, the symptoms may worsen and the acquired hypersensitivity may become irreversible. Hence, the consequences of allergen exposure can be far-reaching. Workers' health should therefore be protected by managing exposure to allergens.

One of the tools available for exposure management is the application of occupational exposure limits (OELs). An OEL is the maximum permissible occupational exposure level to a given airborne substance. OELs are applied by the government and the business community.

OELs are derived from 'toxicology-based recommended occupational exposure limits', which are based on scientific knowledge. One example of the latter type of exposure limit is a 'health-based recommended occupational exposure limit' for a non-carcinogenic substance. Such a limit specifies a level of exposure to an airborne substance, a threshold level, at or below which it may reasonably be expected that there is no risk of adverse health effects.

However, the validity of using the established procedures and methods to calculate health-based OELs for allergens has been questioned. Of particular significance in this regard is the question of whether it is possible to determine a threshold level. There are grounds for believing that any exposure, however

small, entails *some* risk of sensitisation and of developing allergic respiratory disorders if exposure continues.

At the request of the Minister of Social Affairs and Employment, a specially convened committee of the Health Council has sought to identify the best procedure and method for calculating recommended OELs for allergens which are inhaled in the workplace. In addition, the committee has considered whether the introduction of periodic screening would reduce the impact of these allergens on workers' health.

Without intervention, sensitisation leads to respiratory allergies

Allergy is a hypersensitivity reaction that is initiated by a specific immune response to a foreign agent, an allergen, at an exposure level that is normally tolerated. One of its characteristics is increased sensitivity of the immune system (sensitisation), induced by earlier exposure. Sensitisation may be asymptomatic, insofar as the sensitised individual experiences no physical symptoms. Several instances of exposure may be required before evidence of allergic sensitisation is seen. The risk on sensitisation differs among individuals; genetic predisposition plays a role in that.

In a sensitised person, renewed exposure may ultimately lead to allergic respiratory symptoms (*i.e.*, allergic rhinitis, rhinoconjunctivitis, and asthma). It has been observed that, if exposure continues after sensitisation, symptomatic conditions are liable to develop in several dozen percent of cases. The committee therefore makes the precautionary assumption that, in the event of continued exposure, almost all sensitised workers will ultimately develop allergic respiratory disorders.

Allergic respiratory disorders may lead to irreversible health problems

Allergic respiratory symptoms may be mild to begin with, but become more serious as exposure continues. The respiratory symptoms associated with allergy are not unique to allergy; definite diagnosis therefore requires immunological testing.

It is also possible for symptoms to become chronic, and not disappear when exposure is discontinued. For instance, it is estimated that about half of the workers who develop occupational allergic asthma still experience asthmatic symptoms years after exposure has ceased.

However, the sooner diagnosis is made after the appearance of symptoms, and the sooner exposure is ended, the better the prognosis is. The long-term

avoidance of exposure can even lead to the disappearance of detectable sensitisation. However, in most cases, once a person has been sensitised, he or she will remain hypersensitive for the rest of his or her life and liable to develop the same allergic respiratory symptoms in the event of renewed exposure to the relevant allergen. No curative treatment is currently available to reverse this hypersensitivity.

Respiratory allergy is a contributor to disease burden both at the personal level and at societal level. It also reduces quality of life, as reflected in physical, social and daily well-being, by affecting things such as career prospects, the presence of physical and mental problems, absenteeism and work disability.

Various agents can induce an allergy

There is a great variety of compounds, which cause allergic respiratory disorders in the workplace. They are divided into those with a high molecular weight and those with a low molecular weight.

The first group consists mainly of proteins, such as those found in (wheat) flour, and the urine of laboratory animals. Such allergens mainly induce a direct immune response by an IgE-mediated mechanism. The second group consists mainly of small compounds, such as acid anhydrides and isocyanates. Immune responses are provoked only when such allergens are bonded to proteins found in the body, such as serum albumin.

The different types of allergen differ in their ability to induce an immune response. It is not yet entirely clear what factors are responsible for the differences, but it is known that the physical and chemical characteristics and other intrinsic properties of the allergen play a role.

The circumstances of exposure also may vary enormously. For instance, workers are often exposed to mixtures of allergens. When working with wheat flour dust, for instance, or using gloves containing natural latex powder, a worker can be simultaneously exposed to dozens of different wheat flour dust or latex allergens, which are released into the air.

Other factors play a role as well

Exposure to an allergen is the key event in the development of an occupational respiratory allergy. However, various other factors may also influence the development of such an allergy. These include exposure conditions, exposure pattern and simultaneous exposure to other substances.

Furthermore, personal factors, such as genetic predisposition, lifestyle, infections, and the fact that exposure outside the workplace may have occurred earlier, can increase the risk for developing an allergy.

In practice, it is difficult to quantify the significance of these risk factors for the development of occupational respiratory allergies, simply because not enough is yet known.

Respiratory allergies are common in certain working populations

In certain industries, the risk for developing allergic respiratory symptoms due to occupational inhalation of allergens is relatively high. These include people working in the baking and flour-processing industries, laboratory animal care, and the bell pepper and flower greenhouse cultivation industry, as well as people who are exposed to industrial enzymes, soluble platinum salts, isocyanates or acid anhydrides at work. Epidemiological data from these types of industries suggest that the risk may amount to several dozen percentage points, depending on the type of allergen and other factors. Hence, a substantial proportion of workers who are exposed to airborne allergens at work develop specific sensitisation and allergic respiratory diseases.

Sensitisation is the best basis for the calculation of toxicology-based OELs

An occupational exposure limit is based on the most 'critical' adverse health effect associated with the relevant substance. The critical effect may be the effect that is first observed when exposure increases, or the effect that is most significant in the development of disease.

Where allergic respiratory disorders are concerned, the committee is of the opinion that allergic sensitisation should be regarded as the critical effect. Allergic sensitisation is the best starting point for the calculation of OELs, since it plays a crucial biological role and is a prerequisite for the development of allergy. Once sensitisation has occurred, continued exposure will lead to allergy in most cases.

An exposure level below which no sensitisation develops can exist

Current scientific knowledge regarding the relevant allergic immunological mechanisms leads the committee to believe that it is plausible that a threshold level exists, below which no allergic sensitisation may be expected. This level

may be very low: so low, in fact, that little of an allergen is needed to provoke an allergic immune response.

Where a few allergens were concerned, the committee considered whether threshold levels could be deduced from the available epidemiological data. This does appear to be possible where soluble platinum salts are concerned. However, no evidence of a threshold level was observed for (wheat) flour dust, even at low levels of exposure. More detailed study is needed before conclusions may be drawn regarding other allergens.

Furthermore, the results of animal studies provide a mixed picture. For instance, a threshold level was observed in a few experiments, but in others not. The committee emphasises, however, that the outcomes of the animal experiments need to be interpreted cautiously, since the experimental exposure conditions tend to differ considerably from workplace exposure conditions. The design of the animal inhalation models could be improved as well.

Preferably health-based occupational exposure limit should be derived

Current knowledge suggests that a threshold level does exist for inhaled allergens. This implies that health-based recommended occupational exposure limits can be calculated for allergens using the same procedures and methods as those used for other non-carcinogenic substances. Hence, the first step towards calculating such a limit is to determine whether, in the given instance, it is possible to use a method such as the common no-observed-adverse-effect-level method, the benchmark dose method, or another similar statistical model for human data.

However, the committee believes that, where most allergens are concerned, it will not be possible to calculate a reliable health-based recommended occupational exposure limit by any such method. The reason being that, in most cases, the threshold level will be too low to discern using the techniques presently available.

If that is not possible, a reference value can serve as an alternative

The committee therefore proposes an alternative approach for those allergens for which no reliable health-based recommended OEL can be calculated by the established methods. This approach involves determining reference values, *i.e.* concentration levels that correspond to predefined accepted levels of risk of allergic sensitisation.

These reference values can then be used as a basis for assessing occupational exposure limits. The committee recommends that the predefined accepted level

of risk should take account of the background prevalence of the allergen in question. However, the final decision on the predefined accepted level of risk will also depend on policy and social considerations.

Periodic screening for allergic sensitisation can be an useful additional tool

Although occupational exposure limits are useful as a means of protecting workers' health, it should be taken into account that cases of allergic sensitisation and respiratory disorder can happen. One additional option available to the government and the business community is the early detection of sensitised workers, by means of periodic screening, for example.

In view of the prognosis associated with continued exposure and the high prevalence of allergic respiratory disorders in some occupational groups, the committee considers periodic screening for allergic sensitisation to be a potentially valuable tool – provided that workers are properly informed about the potential consequences of a positive test result. The latter proviso is important because, in the most extreme cases, the detection of sensitisation could have very far-reaching consequences for a worker.

The feasibility of periodic screening should be considered on a case-by-case basis

The committee, however, makes some comments on the feasibility of periodic screening in the workplace. For instance, periodic screening is of value only where accurate and reliable tests are available for the detection of allergic sensitisation to the relevant allergen. Such tests are available for certain well-known allergens, such as those found in flour dust, the urine of laboratory animals and in latex. Where other allergens are concerned, however, such tests still need to be developed. The allergens in question include those that can cause sensitisation by triggering a non-IgE-mediated immune response. As long as these immunological tests are not available, screening may focus on the detection of early symptoms and signs caused by allergy.

Another criterion is that periodic screening is performed at an acceptable price. In view of the number of cases of allergic respiratory symptoms in certain occupational groups, the committee assumes that screening is likely to be cost-effective for such groups. However, there is insufficient evidence to confirm that this is indeed the case, because no thorough cost-effectiveness studies have yet been performed.

In conclusion, the committee judges that it is worth to consider the introduction of periodic screening in addition to other tools available in managing exposure. Basically, periodic screening could be fairly and straightforwardly incorporated into the already existing, and statutory regulated periodic occupational health examination. The feasibility of periodic screening on allergic sensitisation, and what else is needed to comply with the most important criteria, should however be judged case-by-case.

Research requirements

At the moment, only for a small number of allergens sufficient toxicity and effectiveness studies are performed. For this reason it is important to stimulate research on other allergens. Also the development of reliable methods to measure exposure and of immunological tests demands attention. Furthermore, there is a need for information on the suitability of periodic screening.

Education and training of radiation protection experts

Health Council of the Netherlands. Education and training of radiation protection experts. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/06E. ISBN: 978-90-5549-704-1 (in Dutch and English)

It is time for an evaluation of the system for radiation protection training

Exposure to ionising radiation may lead to damaging health effects. That is why individuals who use radioactive materials or equipment that emits ionising radiation, as well as those responsible for supervising them, must receive suitable training on the subject of radiation protection. Dutch legislation in this area is currently being revised as a result of new European directives on radiation protection.

Within the framework of this process, the State Secretary of Social Affairs and Employment asked the Health Council of the Netherlands to advise on the optimal system for training radiation protection experts, the requirements for such a system, and the proficiency requirements for educational curricula and continuing education programmes. The State Secretary also asked whether all persons with a valid certification in radiological protection must be included in the legally required register of radiation experts, or whether a smaller selection of these individuals will suffice. In this advisory report, the Standing Committee on Radiation and Health of the Council (hereafter referred to as 'the Committee') provides answers to these questions.

Different training is required for experts and qualified professionals

The Committee has come to the conclusion that the current educational and training system includes a number of positive elements that should be maintained. However, it is important to record the responsibilities and related educational requirements for each function more clearly than is currently the case. To this end, the Committee suggests differentiating between two groups of workers:

- radiation protection experts, who are also responsible for radiological protection measures in businesses or institutions, and
- radiological protection-qualified practitioners, capable of working with ionising radiation safely within the limits of their own jobs.

Radiation protection experts have both broad and specific knowledge of this area. They are responsible for the radiation protection of employees and the environment wherever ionising radiation is used within the company or organisation they work for. They are the individuals who qualify for registration as 'experts' as defined by the Decree on Radiation Protection; to this end, the Decree requires inclusion in a registry. As registered experts, they may also act as coordinating and supervising experts.

Radiological protection-qualified practitioners are those individuals who have to deal with one or more specific applications of ionising radiation as part of their job. They have acquired the knowledge required to safely perform certain tasks using sources of ionising radiation or in environments where radiation risks are present, but they are not necessarily considered 'experts' as defined by the Decree on Radiation Protection. However, this is a requirement if they also have supervisory tasks in the field of radiological protection or work independently. In such cases, they must have been trained as radiation protection experts.

Reform of the training system is necessary to accommodate the new classification

The Committee recommends modifying the current education and training system. The Committee suggests two levels of education for radiation protection experts, comparable to the current level 3 and 2 training, to be named 'Basic Radiation Protection Expert' and 'Top Radiation Protection Expert'. These courses should provide a general, broad education in radiological protection.

The 'Basic' training is modelled on the level 3 training, but without the link to working in a C-laboratory^{*}; the training provides a sufficient basis for working as a radiation protection expert, including knowledge of open and closed sources and an understanding of organisational, procedural and administrative aspects.

The 'Top' training is the current level 2 training, a deeper and broader education than the 'Basic' curriculum.

Clearly defined criteria must apply to the level and content of the training. The Committee recommends that these educational objectives be determined by the Board of Experts on Radiation Expert Registration once this Board has been formally established and to secure this task for the Board. Additionally, the Committee recommends legislating that educational objectives must include organisational, procedural and administrative aspects.

Regarding radiological protection-qualified practitioners, a differentiation should be made between general and specific training. The Committee suggests naming the general training courses 'Basic Radiological Protection' and 'Advanced Radiological Protection'. These courses can be modelled on the current level 5 and 4 training. The Committee also recommends further differentiation into 'A' (only knowledge of closed sources of radioactivity) and 'B' courses (knowledge of open and closed sources).

It is desirable that certain professions are not given a general training course, but one tailored to the profession. The Committee proposes to create such courses named 'Radiological Protection for (the profession in question)'. These courses should, where necessary, become an integral part of vocational education curricula.

These courses must also meet clearly defined criteria for level and content. The Committee recommends that the educational objectives for the general training courses be determined by the Board of Experts on Radiation Expert Registration and to secure this task for the Board. The educational objectives for these courses only need to include limited organisational, procedural and administrative aspects, that are tailored to practice.

Regarding profession-specific training courses in radiological protection, the Committee recommends including the educational objectives at the national level in the vocational education curricula, in consultation with radiation protection experts. These practical vocational courses in radiological protection do not

* A C-laboratory is a laboratory where working with open radioactive sources is permitted and that is categorised as class C, the lightest of three classes, based on a 1962 advisory report by the Health Council. In the 'Guidelines for accreditation of training regarding radioactive materials and appliances of 20 November 1984', the level 3 training is specifically focused on expertise relating to working with open radioactive materials in a C-laboratory.

need to include organisational, procedural or administrative aspects, with the exception of courses for professions wherein one may bear the responsibility for complying with licensing demands.

Continuing education programmes also need to be arranged by type of training

The Committee recommends periodical re-registration of registered radiation protection experts. By making continuing education programmes mandatory for re-registration, it is secured that knowledge is kept up to date. The nature of this further training depends on the level of expertise, and could be (also) organised by the Netherlands Society for Radiological Protection.

Continuing education for radiological protection-qualified practitioners should be organised by the professional societies. Additionally, where applicable, it is the responsibility of the license holder to ensure adequate and sufficient continuing education.

For groups of medical radiological protection-qualified practitioners that must be registered in accordance with the Individual Health Care Professions Act (BIG Act), the registration and re-registration currently dictated by the BIG Act is not suitable for ensuring proficiency, because it does not ask about continuing education. The BIG Act does leave room for this possibility. The Committee recommends modifying the requirements for re-registration in accordance with the BIG Act so as to include sufficient continuing education as a condition for re-registration. Additionally, quality visitation within medical professions may play an important controlling role, as may inspections by the Netherlands Health Care Inspectorate.

The scientific expertise declines

The Committee draws special attention to the decline in scientific expertise in the field of radiological protection. Sufficient numbers of qualified trainers are required for solid educational and training programmes.

Personal dosimetry for occupational exposure to ionising radiation

Health Council of the Netherlands. Personal dosimetry for occupational exposure to ionising radiation. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/07E. ISBN: 978-90-5549-703-4 (in Dutch and English)

Radiological protection care is necessary

Some workers may be exposed to ionising radiation while exercising their duties because they work with or in the vicinity of equipment or substances that emit radiation. Exposure to ionising radiation may lead to adverse health effects. Therefore, adequate radiological protection is desirable for the workers involved. To safeguard a high degree of protection, this care must be tailored to suit specific needs.

Personal dosimetry is a key tool

The regulations defined in the Decree on Radiation Protection are designed to protect workers in the Netherlands from the negative effects of exposure to ionising radiation. The decree includes provisions stipulating that the maximum allowed annual dose for those who are classified as 'exposed worker' may be higher than for other workers. It also prescribes specific protection and monitoring measures.

One of these measures is that 'exposed workers' must wear a so-called personal dosimeter. This allows the received radiation dose to be recorded for each individual worker. This is important in order to check whether the dose remains within the limits set and whether exposure has been kept as low as reasonably possible.

Which workers require routine personal dosimetry?

In practice, the requirement for wearing personal dosimeters was implemented broadly in the Netherlands. This meant that all workers that work with sources of ionising radiation were equipped with personal dosimeters, even if they were exposed to so little radiation that they were not formally to be classified as 'exposed workers'.

There have been recent changes to this standard practice, however. Some large institutions have decided to classify fewer employees than previously as 'exposed workers', and no longer provide them with personal dosimeters. They feel routine personal dosimetry is unnecessary in these cases.

This prompted the Secretary of State for Social Affairs and Employment to ask the Health Council of the Netherlands for advice regarding the possibility of routinely providing fewer workers with personal dosimeters. Does the law allow for this change of practice? Is this allowable in terms of health? And what conditions must be met if a decrease is to be permissible? In this advisory report, the Standing Committee on Radiation and Health provides answers to these questions.

Abandoning personal dosimetry is allowable for certain workers

Changing the policies regarding who is required to wear a personal dosimeter is possible, and workers who are not actually exposed – even if they work with or in the vicinity of equipment or materials that emit ionising radiation – do not automatically need to be considered 'exposed workers'. This releases them from the obligation of wearing a personal dosimeter. Specifically, this might include groups of workers for which it has been demonstrated that:

- the degree of exposure, including any disruptions that may reasonably be anticipated, is consistently very low (less than 0.2 millisievert per quarter), and also
- the odds of abnormal events and the potential for significantly higher exposure (more than 0.2 millisievert per event) are low.

There are no legal issues with this liberalisation of personal dosimetry policy, because it meets national and international standards. After all, the classification as 'exposed worker' is still based on the degree of exposure to be expected in daily practice. There are also no health concerns standing in the way of no longer wearing a personal dosimeter.

Additional measures for these workers are desirable

In order to decrease the number of workers with personal dosimeters in a responsible fashion, a number of conditions must be met. The basic tenet is that anyone who may be exposed to ionising radiation during work is entitled to adequate personal radiation protection. This position is in agreement with previous Health Council recommendations on the subject.

Therefore, the recommendation is to create a new category of workers: category C. This category includes workers who are not classified as 'exposed worker', but who do work with or near equipment or substances that emit ionising radiation.

This is because they normally only experience minimal exposure, but do run the risk of being exposed to a not insignificant dose of radiation in the event of a calamity or incident. After all, they will partly be working in a zone defined as 'controlled' or 'monitored' under the Decree on Radiation Protection, where such events may occur. Therefore, they differ from workers who never work in the vicinity of sources of ionising radiation.

Exposure monitoring remains important for these new category C workers. However, this does not necessarily have to involve routine personal dosimetry. The workplace monitoring systems for monitored and controlled zones dictated by the Decree on Radiation Protection are sufficient. Additionally, a programme for radiation protection must be developed for these workers, potentially within the framework of a safety management system, in order to:

- evaluate and test whether measures and facilities for radiation protection of workers are adequate;
- verify that the criteria for classification as category C workers are met;
- determine exposure in abnormal situations or in the event of a radiological accident.

This radiation protection programme must be implemented by or under supervision of radiation protection experts.

These regulations will sufficiently formalise and secure the protection of this group of workers, while at the same time underlining the employer's own responsibilities.

A good risk analysis contributes to good protection

An adequate risk analysis is important to ensure that workers are assigned to the correct category. There are signs that current risk analyses are not always of suf-

ficiently high quality. The creation of a new category of workers requiring a separate form of monitoring and protection only serves to emphasize the importance of ensuring proper categorisation. A number of concrete conditions have been formulated to this end.

For example, a good risk analysis must provide insight into the degree of personal exposure workers may experience while performing their duties. The presence and use of all potential radiation sources must be considered. When determining the odds and degree of potential exposure, measures taken to limit exposure and prevent accidents must also be taken into account. The involvement of a radiation protection expert in drafting the risk analysis is required for these reasons.

In addition to the dose to be expected under normal working and operating conditions, the odds of incidents and the likelihood workers will be exposed to radiation in the event of such incidents must be considered separately.

If these conditions are met, assignment of workers to a category will occur based on actual or risk of exposure wherever possible. Protective measures will also be suited to their situation, whether that involves routine personal dosimetry or not.

Heat stress in the workplace

Health Council of the Netherlands. Heat stress in the workplace. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/24. ISBN: 978-90-5549-735-5 (in Dutch)

The request for advice

In the present report, at the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands has investigated whether at the present time there are any new scientific insights concerning health-based and safety-based limit values for heat stress in the workplace, and whether any such insights can be expected in due course. This report is the first in a series of reports examining occupational risks covered by the Working Conditions Act and its associated regulations. In order to be able to answer the Minister's questions, the Committee studied scientific data on the adverse short-term and long-term effects of heat stress. In this report, the Committee makes no proposals concerning the level of a limit value.

Heat stress in the workplace

Heat stress in the workplace is not simply a question of ambient temperature. An equally important factor is the degree of effort associated with the work in question, since this can result in the production of considerable amounts of body heat. Can such body heat easily be dissipated to the immediate environment, or is this process impeded by clothing? In addition, the response to heat stress varies from one person to another. At the individual level, acclimatisation and fitness are the main factors that reduce an employee's susceptibility to heat stress.

Limit values and the effects of heat stress

The Netherlands has no statutory limit values for heat stress. There is a set of reference values, however, which is used for the purpose of compliance. These are described in NEN-ISO 7243: 1989. At international level, the most widely known limit values are those that were recommended by the American National Institute for Occupational Safety and Health (NIOSH). Both the NIOSH-values and the reference values are based on the prevention of acute heat illnesses (such as heat exhaustion and heat-stroke), which involves using body core temperature as an indicator.

A survey of the scientific literature reveals that research into heat stress has mainly focused on its adverse short-term physical effects. The bulk of these studies were carried out under controlled conditions. The amount of research data relating to realistic work situations is very limited indeed.

Results from more recent scientific research show that heat stress also causes adverse short-term mental effects. Reduced vigilance and poorer performance in terms of other mental functions were observed at environmental heat levels at which there was still no indication of adverse physical effects. The scientific literature indicates that heat stress results in an increased incidence of unsafe acts and a greater risk of accidents. In work situations, effects of this kind can endanger the health of an individual or that of others.

Conclusions and recommendations in relation to limit values

Reference values for the adverse short-term physical effects of heat stress do not need to be reviewed

The Committee concludes that, at the present time, there are no new scientific insights concerning the adverse short-term physical effects of heat stress. There is, therefore, no reason to review existing health-based limit values, such as the NEN-ISO reference values.

Reference values do not take adverse short-term mental effects into account

The reasoning which underpins the reference values and limit values recommended by NIOSH makes no allowance for any adverse short-term mental effects of heat stress. The Committee takes the view that current scientific knowledge

appears to offer sufficient opportunities for the establishment of safety-based limit values for heat stress.

There is insufficient data about the long-term effects of heat stress

Too few studies have been conducted on the adverse long-term physical and mental effects of heat stress. The Committee takes the view that current scientific knowledge on long-term effects is not an adequate basis for health-based or safety-based limit values.

2,4,5-Trimethylaniline

Health Council of the Netherlands. 2,4,5-Trimethylaniline; Evaluation of the carcinogenicity and genotoxicity. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/01OSH. ISBN: 978-90-5549-686-0 (in English)

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Standards of the Health Council, hereafter called the committee. In this report, the committee evaluated 2,4,5-trimethylaniline. The agent has been used as an intermediate for dyestuffs and pharmaceuticals.

Based on the available information, the committee is of the opinion that 2,4,5-trimethylaniline *should be considered as carcinogenic to humans*. This recommendation is comparable to the EU classification in category 2. The committee is furthermore of the opinion that 2,4,5-trimethylaniline acts by a stochastic genotoxic mechanism.

2-Nitroanisole

Health Council of the Netherlands. 2-Nitroanisole; Evaluation of the carcinogenicity and genotoxicity. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/02OSH. ISBN: 978-90-5549-687-7 (in English)

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Standards of the Health Council, hereafter called the committee. In this report, the committee evaluated 2-nitroanisole. 2-Nitroanisole is used in the synthesis of azo dyes, and as an intermediate for the preparation of pharmaceuticals.

Based on the available information, the committee is of the opinion that 2-nitroanisole *should be considered as carcinogenic to humans*. This recommendation is comparable to the EU classification in category 2. The committee is furthermore of the opinion that 2-nitroanisole acts by a stochastic genotoxic mechanism.

4-Vinylcyclohexene diepoxide

Health Council of the Netherlands. 4-Vinylcyclohexene diepoxide; Evaluation of the carcinogenicity and genotoxicity. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/03OSH. ISBN: 978-90-5549-688-4 (in English)

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Standards of the Health Council, hereafter called the committee. In this report, the committee evaluated 4-vinylcyclohexene diepoxide. The agent is used as a diluent for other diepoxides and for epoxy resins

Based on the available information, the committee is of the opinion that 4-vinylcyclohexene diepoxide *should be considered as carcinogenic to humans*. This recommendation is comparable to the EU classification in category 2. The committee is furthermore of the opinion that 4-vinylcyclohexene diepoxide acts by a stochastic genotoxic mechanism.

4-Vinylcyclohexene

Health Council of the Netherlands. 4-Vinylcyclohexene; Evaluation of the carcinogenicity and genotoxicity. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/04OSH. ISBN: 978-90-5549-689-1 (in English)

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Standards of the Health Council, hereafter called the committee. In this report, the committee evaluated 4-vinylcyclohexene. The agent is used for various industrial purposes.

Based on the available information, the committee is of the opinion that 4-vinylcyclohexene *should be considered as carcinogenic to humans*. This recommendation is comparable to the EU classification in category 2. The committee is furthermore of the opinion that 4-vinylcyclohexene should be considered a genotoxic agent that acts by a stochastic mechanism.

Arsine

Health Council of the Netherlands. Arsine; Evaluation of the carcinogenicity and genotoxicity. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/05OSH. ISBN: 978-90-5549-690-7 (in English)

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Standards of the Health Council, hereafter called the committee. In this report, the committee evaluated arsine. The agent is used for various industrial purposes.

Based on the available information, the committee is of the opinion that arsine has been insufficiently investigated. While the available data do not warrant a classification as carcinogenic to humans or as should be regarded as carcinogenic to humans, they indicate that there is cause for concern. Therefore, the committee recommends classifying arsine as *a suspected human carcinogen*. This recommendation is comparable to the EU classification in category 3. The situation is, furthermore, comparable with subcategory b of this category.

Ifosfamide

Health Council of the Netherlands. Ifosfamide; Evaluation of the carcinogenicity and genotoxicity. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/06OSH. ISBN: 978-90-5549-691-4 (in English)

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Standards of the Health Council, hereafter called the committee. In this report, the committee evaluated ifosfamide. Ifosfamide is used as an antineoplastic and immunosuppressive drug.

Based on the available information, the committee is of the opinion that ifosfamide *should be considered as carcinogenic to humans*. This recommendation is comparable to the EU classification in category 2. The committee is furthermore of the opinion that ifosfamide acts by a stochastic genotoxic mechanism.

n-Butyl glycidyl ether

Health Council of the Netherlands. n-Butyl glycidyl ether; Evaluation of the carcinogenicity and genotoxicity. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/07OSH. ISBN: 978-90-5549-692-4 (in English)

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Standards of the Health Council, hereafter called the committee. In this report, the committee evaluated n-butyl glycidyl ether. The agent has various uses, such as in the production of epoxy resins.

Based on the available information, the committee is of the opinion that n-butyl glycidyl ether has been insufficiently investigated. While the available data do not warrant a classification as carcinogenic to humans or as should be regarded as carcinogenic to humans, they indicate that there is cause for concern. Therefore, the committee recommends classifying n-butyl glycidyl ether as *a suspected human carcinogen*. This recommendation is comparable to the EU classification in category 3. The situation is, furthermore, comparable with subcategory b of this category.

p-Nitroaniline

Health Council of the Netherlands. p-Nitroaniline; Evaluation of the carcinogenicity and genotoxicity. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/08OSH. ISBN: 978-90-5549-694-5 (in English)

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Standards of the Health Council, hereafter called the committee. In this report, the committee evaluated p-nitroaniline. p-Nitroaniline is used as an intermediate in the production of different substances, including antioxidants and dyes.

Based on the available information, the committee is of the opinion that p-nitroaniline has been insufficiently investigated. While the available data do not warrant a classification as carcinogenic to humans or as should be regarded as carcinogenic to humans, they indicate that there is cause for concern for man.

Therefore, the committee recommends classifying p-nitroaniline as *a suspected human carcinogen*. This recommendation is comparable to the EU classification in category 3. The situation is, furthermore, comparable with subcategory b of this category.

Stibine

Health Council of the Netherlands. Stibine; Evaluation of the carcinogenicity and genotoxicity. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/09OSH. ISBN: 978-90-5549-696-9 (in English)

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Standards of the Health Council, hereafter called the committee. In this report, the committee evaluated stibine. Stibine is used as dopant in the microelectronics industry, and is released during charging of lead-acid batteries.

The committee concludes that stibine cannot be classified, due to a lack of carcinogenicity data.

Trichlormethine hydrochloride

Health Council of the Netherlands. Trichlormethine hydrochloride; Evaluation of the carcinogenicity and genotoxicity. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/10OSH. ISBN: 978-90-5549-697-6 (in English)

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Standards of the Health Council, hereafter called the committee. In this report, the committee evaluated trichlormethine hydrochloride. The agent is used as a cytostatic agent in the treatment of cancer and arthritis, and is furthermore used in the production of textile dyes.

Based on the available information, the committee is of the opinion that trichlormethine hydrochloride *should be considered as carcinogenic to humans*. This recommendation is comparable to the EU classification in category 2. The committee is furthermore of the opinion that trichlormethine hydrochloride acts by a stochastic genotoxic mechanism.

Occupational exposure to organic solvents: effects on human reproduction

Health Council of the Netherlands. Occupational exposure to organic solvents: effects on human reproduction. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/11OSH. ISBN: 978-90-5549-716-4 (in English)

Dutch study poses questions for Health Council

It is estimated that half a million workers in the Netherlands are regularly exposed to organic solvents. Some examples of well-known solvents are toluene, styrene, xylene, benzene and turpentine. These are widely used for degreasing and diluting, and are found in such products as ordinary paints, car paints, stains, and glues. Solvents evaporate, so those who work with these products tend to inhale them.

It is known for a long time that inhaling organic solvent fumes may impair people's health. In recent years, occupational exposure to these solvents has been linked to various effects. The most well-known and best documented effect is the occurrence of chronic toxic encephalopathy (CTE), also known as organic psycho syndrome (OPS). This involves serious damage to the nervous system, resulting in memory disorders, impaired concentration, mental inertia, fatigue, headache, irritability and depression. In addition, it is known that exposure to certain organic solvents (such as benzene) can cause cancer.

Less is known about possible effects on reproduction. In 1999, that topic was at the centre of a commotion, following the publication of a Dutch study in men who had been examined at a fertility clinic. This study found that exposure to organic solvents appeared to be linked to reduced sperm quality. The results of this study led to questions being asked in the Dutch parliament. The results of another Dutch study were published in 2005. These results suggested that expo-

sure to solvents might cause birth defects among the children of professional painters.

In 2005, these two Dutch studies caused the State Secretary for Social Affairs and Employment to seek the Health Council's advice about the possible effects on reproduction of occupational exposure to organic solvents. The following questions were submitted to a specially appointed committee:

- Is there any evidence that occupational exposure to organic solvents can produce effects on reproduction?
- Is there a known mechanism of action that could explain these possible effects?
- Do the limit values* that currently apply to various organic solvents provide protection against effects on reproduction?

The Committee uses the term "reproductive disorders" to refer to any problems that may arise in connection with fertility, pregnancy, and development of the offspring.

Half of the available research is useable

Requests for advice are answered by assessing and weighing up the results of scientific research. One key finding is that, while there are many publications dealing with the effects of occupational exposure to solvents on reproduction, only a few of them can be used for answering the committee's questions. For example, exposure to solvents is often difficult to quantify. One of the major problems is that, in nearly every case, the employees in question are exposed to mixtures of different solvents. Furthermore, workers in many industries also come into contact with other substances (such as metals), which can sometimes cause reproductive disorders. In such cases, it is no longer possible to identify the relation between exposure to a given solvent and the occurrence of reproductive disorders. In spite of the efforts of research workers in recent years, very little is known about the composition of the mixtures used by people in the course of their work, and about the concentrations of the individual solvents to which they are exposed.

A second problem is that effects can occur at many different phases in the reproductive cycle. This may involve effects on sperm, ova, ovaries, and menstruation, as well as the occurrence of miscarriages, birth defects, and problems

* The 2005 request for advice refers to the MAC values (Maximum Allowed Concentrations). In 2007, these values were substituted by public and private occupational exposure limits.

in the child's psychomotor development. These effects all involve different mechanisms and, in all probability, a range of different causes. Therefore, for all studies it is essential to draw a distinction between the different effects and to define each effect accurately.

Finally, there is often no information available about the timing of exposure, even though this is thought to be one of the critical factors in causing toxic effects on the reproductive system. For example, effects of exposure at an early stage of pregnancy can differ from those resulting from exposure at a later stage.

As a result of these weaknesses, the quality of much epidemiological research is too poor to enable judgments about the reported links between exposures and reproductive disorders. After evaluating the available studies, the committee has rejected more than half of them. This still left well over 80 studies which did meet the quality criteria.

Effects on reproduction were identified for a number of solvents and situations

Exposure to some ethylene glycol ethers impairs male fertility

After examining studies in human subjects, the committee found indications that exposure to various ethylene glycol ethers (EGEE* and EGME**) may impair male fertility. This has been confirmed by experimental animal studies.

Workers exposed to ethylene glycol ethers include those carrying out painting or maintenance work, and those employed in the semiconductor industry. Studies of employees in the painting and maintenance trade show weak indications for an increased risk of fertility problems in men, depending on the level of exposure (probably to ethylene glycol ethers). The introduction of appropriate regulations caused exposure levels to these glycol ethers in Dutch companies to fall markedly in recent years. In addition, a switch was made from using ethylene glycol ethers (such as EGEE and EGME) to using other less harmful glycol ethers. However, recent exposure data are not available. For this reason, the committee cannot exclude the possibility that employees in some sectors may still be at risk for harmful effects on reproduction as a result of exposure to these ethylene glycol ethers.

* EGEE: Ethylene glycol ethyl ether or 2-ethoxyethanol.

** EGME: Ethylene glycol methyl ether or 2-methoxyethanol.

Exposure of pregnant women to some ethylene glycol ethers increases the risk of spontaneous abortions and birth defects

Exposure of pregnant women to ethylene glycol ethers may lead to reproduction toxic effects. Epidemiological studies give indications for an increased risk of spontaneous abortions and malformations after exposure to EGME and EGEE. In addition, experimental animal studies convincingly demonstrated that exposure to ethylene glycol ethers gives causes harmful effects during and after pregnancy (ranging from foetal death to birth defects).

Ethylene glycol ethers are primarily used in the semiconductor industry. Human studies in this industry also provide indications for an increased risk of such effects. Here too, exposure levels have fallen substantially, but the committee cannot exclude the possibility that there are still companies where the airborne concentrations of these substances could exert an effect on the development of the progeny.

Exposure of pregnant women to tetrachloroethylene (PER) and xylene may increase the risk of miscarriage

The committee concludes that there are weak indications that exposure to tetrachloroethylene (PER) and xylene in pregnant women increases the risk of spontaneous abortions. Experimental animal studies also show that exposure to these solvents may harm the unborn foetus. However, the evidence is not strong enough to confirm the epidemiological data.

Exposure to PER is mainly found in dry-cleaning shops (chemical laundries). Studies carried out among employees of dry-cleaning shops and laundries in the 1980s confirm the perception that there might be an increased risk of miscarriage, probably due to exposure to high concentrations of PER. However, PER exposure levels have dropped so markedly in recent years that the committee does not expect current exposure levels to lead to effects on reproduction.

Exposure to xylene mainly occurs in printing companies and in the petrochemical industry. Because the subjects in the available studies were simultaneously exposed to other solvents, the committee is unable to determine whether there is still an elevated risk for those who are currently employed in these industries.

Exposure of men and pregnant women to toluene increases the risk of spontaneous abortion

The committee concludes that there are indications from studies in human subjects that exposure of pregnant women to toluene increases the risk of spontaneous abortion. There are also weak indications for an increased risk of childhood leukaemia. Data from experimental animal studies do not confirm a possible link between exposure to toluene and the occurrence of spontaneous abortions. However, the evidence in these studies is limited and not sufficient for definite conclusions.

Aside from exposure to xylene, those working in printing companies and in the petrochemical industry may also be exposed to toluene. The committee concludes that there are weak indications that pregnant female employees working in printing companies or the petrochemical industry who are exposed to agents such as toluene, amongst others, have an elevated risk of reproductive disorders. As these women are also exposed to other solvents (e.g. xylene and styrene), it is impossible to determine which proportion of that risk can be attributed to toluene.

It is not just the exposure of pregnant women that may have implications for the offspring. There are also weak indications that if men are exposed to toluene (during painting and maintenance work, for example) prior to conception, their partner is at increased risk of a spontaneous abortions.

No details are available concerning the current concentrations of toluene. Accordingly, the committee is unable to determine whether there is still an increased risk of spontaneous abortions in these industries.

The effects of many solvents are still poorly understood

Information concerning the effects of exposure on reproduction is only available for a small fraction of the total group of organic solvents (toluene, xylene, styrene, acetone, ethylene glycol ethers, tetrachloroethylene, benzene and methylene chloride). For a large group of organic solvents (such as N-methylpyrrolidone, butanol, isopropanol, 2-butoxyethanol and many others) no epidemiological or other research has been carried regarding their effects on reproduction. Although people are regularly exposed to these solvents in practice, the committee cannot make any statements concerning the effects of occupational exposure on reproduction.

Even in the case of those solvents for which data are available, the issue is far from cut and dried. Sometimes, the results are very limited or contradictory.

Therefore, it is impossible to draw any conclusions with regard to these solvents, either.

Current limit values cannot be assessed

Do the limit values which currently apply to various organic solvents in the workplace offer sufficient protection against effects on reproduction? Based on the data which has been examined, the committee is unable to answer this question from the State Secretary. By definition, a health-based recommended occupational exposure limit protects employees (and their offspring) against *all* adverse health effects arising from occupational exposure to substances. Therefore, when determining the health-based recommended exposure limits, the effects on reproduction must also be taken into account. But that would require relevant data to be available, and that is often not the case.

Since the introduction of the new Working Conditions Act on January 1, 2007, both public and private limit values have to be pegged at the same level as the health-based recommended occupational exposure limit. Toluene, acetone, xylene, benzene, and some glycol ethers are examples of solvents which are subject to a legally binding limit. In the case of most other solvents, the social partners (employers and trade union confederations) are responsible for deriving of safe limit values.

The committee therefore believes that if an epidemiological study identifies effects on reproduction, it is important to determine the type and concentration of the solvents to which the individuals in question have been exposed. If these details are lacking, it is impossible to determine whether the identified effects on reproduction are due to exposure at a level above the existing limit values, or that the existing limit values simply do not provide sufficient protection.

Better exposure data are needed to identify the potential risks

For a number of solvents (ethylene glycol ethers, toluene, xylene and tetrachloroethylene), there are (weak) indications that exposure may cause reproductive disorders. However, up-to-date data concerning exposure in various branches of industry are not publicly available. Therefore, the committee recommends the following for these substances:

- first, identify those types of industry in which exposure to these solvents still takes place
 - next, produce quantitative data on the exposure levels of the individual solvents for those types of industry in which exposure is likely.
-

Improved data accessibility is also required

For most solvents, little or no exposure data are available. In the Netherlands, most exposure measurements are done at the behest of individual companies, which means that the data are often not publicly available. Therefore, the committee recommends that a national database be created in which all exposure data could be collected. The systems currently in use in Great Britain or Germany could serve as an example.

In addition, the committee established that current registration systems for recording birth defects also have their limitations. Therefore, the committee also recommends the creation of a single national registry which would incorporate and integrate all existing registers.

Furthermore, if it were possible to link these two databases (for exposure and for effects), numerous opportunities would be provided to investigate risks in the workplace more effectively than is currently possible.

Platinum and platinum compounds

Health Council of the Netherlands. Platinum and platinum compounds. Health-based recommended occupational exposure limit. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/12OSH. ISBN: 978-90-5549-718-8 (in English)

Scope

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands recommends health-based occupational exposure limits for the concentration of toxic substances in the air at the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS).

The present advice on platinum and platinum compounds was prepared in cooperation with the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG), an advisory body of the Nordic countries. The joint report on the consequences of occupational exposure to platinum and platinum compounds, published in Sweden in 1997 (*Arbete och Hälsa* 1997:14) is included in Part II of this document. Part I consists of a summary of the data presented in Part II, presentation of data becoming available since 1997, and a discussion of the consequences of occupational exposure to platinum and its compounds. The conclusions in this advice are based on scientific publications which appeared before September 2007, and are entirely DECOS' view.

Physical and chemical characteristics and use

The report covers metallic platinum (CAS number 7440-06-4) and a number of platinum compounds. Platinum-based drugs (particularly cytostatics/chemotherapeutics like e.g., cisplatin) are not covered.

Platinum is a silver-grey noble metal of high commercial value due to its resistance to corrosive agents and its properties as an oxidation and reduction catalyst. It is obtained from mined ore and recycled metal; refining is done by conversion to hexachloroplatinic acid.

Platinum and its salts are mainly used in the automotive industry (as catalysts in motor car exhausts). It is further used in jewellery, electronics, and (petro)chemical industry, and, in even smaller amounts, in dentistry (bridges, crowns) and in medicine (anti-cancer drugs).

Monitoring

Several organisations, such as the UK Health and Safety Executive (HSE) and the US National Institute for Occupational Safety and Health (NIOSH) and Occupational Safety and Health Administration (OSHA), have described methods that can be used for analysing platinum and platinum compounds in workplace air. Air is filtered. Loaded filters are treated with acid solutions, and the extracts are analysed by specific spectrometric techniques. Generally, lengthy sampling times are required. The methods cannot distinguish between platinum and platinum compounds.

NIOSH has also described methods for analysing platinum in biological samples (blood, tissue, urine).

Limit values

In the Netherlands, there is a legally binding limit for metallic platinum of 1 mg Pt/m³ of air, in line with European Commission directives. There are no limit values for platinum compounds. A number of European countries (Denmark, England, Finland, Norway, Sweden) and US organisations (ACGIH, NIOSH, OSHA) have occupational exposure limits for water-soluble platinum compounds of 2 µg Pt/m³.

Kinetics

Inhalation and oral absorption of platinum metal and the water-insoluble platinum compounds is very low (probably less than 1%). Water-soluble platinum compounds are absorbed to a somewhat higher degree.

Absorbed platinum is distributed to the soft tissues and sometimes also found in the bones. Excretion of bioavailable platinum appears to occur via a biphasic process, mainly in the urine; in humans, the two half lives were ca. 50 hours and ca. 24 days, respectively. Data on biotransformation of platinum or its salts were not found.

Effects in humans

Platinum and water-insoluble platinum compounds

No data are available on the effects on humans following exposure to platinum and insoluble platinum compounds.

Water-soluble compounds

Human data indicate that the most significant risks from occupational exposure to soluble compounds are respiratory sensitisation and skin effects. Especially charged complexes with a halide ligand coordinated to platinum provoked these reactions, while uncharged complexes and soluble complexes in which the halide is present as an ion did not.

In a 5-year prospective cohort study, Merget and co-workers showed a dose-response relationship between airborne soluble platinum-compound concentrations, platinum concentrations in sera of exposed workers, and newly occurring sensitisations. The study was performed in the period 1989-1995, and included a total of 275 employees of a German catalyst-production plant. Water-soluble airborne platinum concentrations were measured in 1992 and 1993, with sampling periods of 12-17 hours. Personal sampling (duration about 8 hours) was performed in 1993 in highly exposed subjects. During the 5-year study period, no new sensitisations occurred in the workers with the no or low exposure. The median concentrations in the 'low-exposure' area were 6.6 and 0.4 ng Pt/m³ in 1992 and 1993, respectively. In the group of 115 highly exposed workers, 14 new sensitisations occurred. The median concentrations in the 'high-exposure' area ranged from 14 to 37 ng Pt/m³. Personal sampling in the highly exposed workers

revealed a median value of 177 ng/m³ with a highest value of 3700 ng/m³. Three measurements (out of 22) exceeded the current threshold limit value of 2000 ng/m³. Smoking cigarettes was positively associated with the development of some work-related allergies.

In a retrospective study of Linnett and Hughes, no allergic reactions were observed in workers occupationally exposed to levels of tetraammineplatinum dichloride mostly below 0.5 µg/m³ but occasionally higher than 2 or 10 µg/m³.

Effects in experimental animals

Generally, the acute toxicity of platinum (compounds) is low and depends on their water solubility: the insoluble salts are less toxic or irritating than the soluble ones.

Platinum and water-insoluble platinum compounds

No experimental animal data are available on the potential eye-irritating or sensitising properties of platinum or insoluble platinum compounds. Platinum dioxide and platinum dichloride were not irritating to the skin.

No data were available from experimental animal inhalation studies. No effects were seen in rats given daily amounts of platinum in the diet of 700 mg/kg bw for four weeks.

For the only insoluble platinum compound tested, viz., platinum dichloride, *in vitro* tests for mutations (mouse lymphoma L5178Y cells) and DNA damage in bacteria (*E. coli*: SOS chromotest) and mammalian cells (human lymphocytes: comet assay) were negative. Both positive and negative results were reported in micronucleus tests in human lymphocytes. The induction of micronuclei was due both to clastogenic and aneuploidogenic mechanisms. Carcinogenicity studies are lacking.

Daily administration of doses of platinum of 0.1-100 mg/kg diet to rats did not induce effects in the fetuses.

Water-soluble platinum compounds

Experimental animal data indicate that soluble platinum compounds are irritating to the skin and corrosive to the eyes. Studies in mice confirmed the sensitising properties of chloroplatinum complexes and the lack of a sensitising potential of tetraammineplatinum dichloride.

No data were available from experimental animal inhalation studies. Oral LD₅₀ values ranged from 10 to 100 mg platinum/kg bw. When soluble salts were administered to rats in the drinking water for four weeks, mainly effects on body weight (decreases) and kidneys (increased weights; impaired functioning) were seen at doses of ca. 50 mg platinum/kg bw. Generally, there were no effects at 10 mg/kg bw/day, but in some studies, there were decreases in haematological values (erythrocyte; haematocrit).

Numerous soluble platinum compounds have been tested for their mutagenic activity *in vitro* in bacterial and mammalian cell systems, mostly without metabolic activation, and in fruit flies. Many of them were positive. Some of them were tested for other end points in other systems (*E. coli*: SOS chromotest; *B. subtilis*: rec assay; human lymphocytes: micronucleus test and comet assay), inducing both positive and negative results. *In vivo*, only dipotassium tetrachloroplatinate and tetraammineplatinum dichloride were tested, showing negative results in an erythrocyte micronucleus test in mice (single oral doses) and in a bone marrow chromosome aberration test in hamsters (repeated oral doses).

Data from carcinogenicity or relevant reproduction toxicity studies are lacking.

Evaluation and advice

Platinum and water-insoluble platinum compounds

Based on the available data, the committee cannot assess the potential genotoxic, carcinogenic, and reproductive effects following exposure to platinum and its insoluble compounds.

DECOS considers the toxicological database for platinum and water-insoluble platinum compounds too poor to recommend a health-based occupational exposure limit.

Water-soluble platinum compounds

Based on the available data, the committee cannot assess the potential genotoxic, carcinogenic, and reproductive effects following exposure to soluble platinum compounds.

The human and experimental animal data available indicate that chloroplatinates provoke sensitising and allergic effects of the respiratory tract and the skin while uncharged complexes and complexes with ligands other than halogens did not.

The committee is of the opinion that the Merget study indicates that there is a threshold for the sensitising effects of chloroplatinates: it does not expect that exposure to levels below 10 ng/m³ causes sensitisation. The committee takes this value as a starting point for deriving a health-based occupational exposure limit. Applying a factor of 2 to account for the relatively small group involved (n=115), the committee recommends 5 ng/m³ as a health-based occupational exposure limit, as an 8-hour time-weighted average. This limit value only holds for chloroplatinates.

Health-based recommended exposure limit

The Dutch Expert Committee on Occupational Standards of the Health Council recommends a health-based occupational exposure limit for chloroplatinates of 5 ng/m³ (as platinum), as an 8-hour time-weighted average concentration.

The committee concludes that the toxicological database does not allow the recommendation of a health-based occupational exposure limit for soluble platinum compounds. However, the committee believes the data of Linnett and Hughes to indicate that an occupational exposure level of 0.5 µg/m³ for tetraammineplatinum dichloride is not associated with toxicity, and might be used as an upper limit for workers.

Gamma-Butyrolactone

Health Council of the Netherlands. Gamma-Butyrolactone; Health-based recommended occupational exposure limit. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/13OSH. ISBN: 978-90-5549-741-6 (in English)

Scope

At request of the Minister of Social Affairs and Employment, the Dutch expert Committee on Occupational Exposure Safety (DECOS), one of the permanent committees of experts of the Health Council, proposes health-based recommended occupational exposure limits for chemical substances in the air in the workplace. These recommendations serve as basis in setting legally binding occupational exposure limits by the minister. In this advisory report, the committee evaluates the consequences of exposure to γ -butyrolactone (GBL), and derives a health-based recommended occupational exposure limit (HBR-OEL).

In a first step the toxicity of the compound is evaluated. This is done in cooperation with the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. The results of the evaluation, which are published in 2004, are included in part 2 of this advisory report. In the first part, the DECOS describes the most relevant data, supplied by newly presented data, and advises on an HBR-OEL. The conclusions of the DECOS are based on scientific papers published before April 2008.

Physical and chemical properties

At room temperature γ -butyrolactone (CAS no. 96-48-0) is a colourless oily liquid with a relatively low vapour pressure, and a mild caramel odour. It is soluble

in water and organic solvents, such as ethanol and benzene. In aqueous solutions, there is a pH-dependent equilibrium between γ -butyrolactone (GBL) and its hydrolysis product γ -hydroxybutyrate (GHB), in which the lactone ring is opened; in acidic conditions GBL dominates, in alkaline conditions GHB.

GBL occurs naturally in certain food products, such as in meat, fruit, coffee, and alcoholic beverages. It is also found in small quantities in the human body.

In the workplace, GBL is used for many purposes, such as: a solvent for polymers and in the electronic industry; as component in chemical paint removers; and, as an intermediary in the production of vitamins, medicines and pyrrolidones. GHB is not only an hydrolysis product of GBL, but it is also processed by the pharmaceutical industry as a medicine. It is namely therapeutically used as sedative, in the treatment of alcohol dependency, in opiate withdrawal syndrome, and in the treatment of narcolepsy.

GBL and GHB is furthermore known as a party drugs, due to their euphoric and sedative properties.

Monitoring and data on exposure

The current methods to detect GBL use a combination of gas chromatography and mass spectrometry. It is possible to separate GBL from GHB, and to quantify them separately by high performance liquid chromatography and UV-visible spectrometry. Furthermore, there are several analysis methods described to quantify GBL and GHB in blood and urine. None of these methods are however standardly applied.

Despite the broad use, there are only a few data on the level of exposure in the workplace. In one investigation airborne exposure levels between 0.01 to 1.1 mg GBL/ m³ have been reported in the breathing zone of workers during removing of graffiti.

Current limit values

In the Netherlands nor elsewhere occupational exposure levels have been set for GBL. In Denmark a provisional exposure level of 50 ppm (180 mg/m³) is applied since 1994.

Kinetics

Gamma-butyrolactone can be absorbed by the body through inhalation, by oral intake or via the skin. Investigations show that the skin has a high permeability for GBL.

In the body, within minutes GBL is converted to GHB by lactonase, an enzyme that is found in the blood and liver. This means that GBL is distributed in the body mainly in the form of GHB. GHB is also an endogenous compound present in mammalian brain.

Both compounds can cross the blood-brain barrier. It is therefore not surprising that they are found in high concentrations in different parts of the brain. Higher concentrations are also measured in the kidneys, the heart, muscles and body fat compared to other body compartments.

GHB is metabolized and eliminated by various routes. One is by entry into the citric acid cycle, which results in carbon dioxide as end product. Another is by formation of γ -aminobutyric acid (GABA), a natural occurring neurotransmitter with inhibitory properties in the brain. The intermediary and end products of GBL are excreted by the body mainly by exhalation (carbon dioxide) and for a smaller part via the urine. In humans, the plasma half-life of GHB, that is the time for half of the substance in plasma to be converted or disappear, ranges between 30 and 60 minutes.

Mechanism of toxicity

Regarding the toxicity of γ -butyrolactone two types of effects are prominent.

The first are neurological effects in the brain. High doses of GBL depress the functioning of the central nervous system. For these effects its hydrolysis products GHB and GABA are thought to be responsible. These compounds bind to receptors in the brain, by which the release of dopamine is inhibited. Dopamine is a neurotransmitter with stimulating properties. Other yet unknown neurotoxic mechanisms might play a role as well.

Secondly, data from animal research suggest that GBL may adversely affect reproduction, but it is not clear yet what kinds of mechanisms cause reproductive toxicity. However, it is supposed that GBL is able to disturb the hormone balance in the brain, and it is suggested that GBL might arrest directly the maturation of unfertilized ovules.

Effects

Observations in humans

Most data on the toxicity of γ -butyrolactone in humans concern acute poisoning after oral intake. No data are known on inhalatory or dermal exposure at work or elsewhere.

GBL, but mainly GHB, are used among youngsters as party drugs. This has led to many case reports of GBL and GHB poisoning. Different types of adverse health effects have been reported. The primary effect is dose-related depression of the central nervous system (CNS), such as sleepiness and loss of consciousness, epileptic seizures, changes in pupillary reflex, uncontrolled movements, confusion, hallucination and euphoria. These effects have been reported at doses of 20 to 30 mg GBL/kg bw (somnolence, dizziness, euphoria), and of about 10 mg GHB/kg bw. A dose of 60 mg GBL/kg bw can induce anesthesia and coma. A near fatal case has been reported of someone who consumed a GBL-containing drink, leading to a dose of about 570 mg GBL/kg bw. Other effects due to oral intake, which are partly related to CNS effects, were also observed, such as decreased heartbeat and blood pressure, nausea, and decreased respiration.

Repeated use of GBL can result in different neurotoxic effects, such as anxiety, depression, tremor, and sleepiness. It is however not clear at what exposure levels these effects occur.

No data are available on possible irritating effects in the skin and the eyes upon exposure to GBL in humans, nor are there any data reported on reproductive toxicity. In addition, there are insufficient reliable data reported on carcinogenicity in humans.

Observations in animals

The few data that are available indicate that undiluted GBL is slightly irritating to the skin, and moderately to severe irritating to the eyes by direct contact.

The dose after a single oral intake at which half of the exposed animals die, is approximately 800 to 1,800 mg GBL/mg bw in mice and rats. This points to a moderate to low acute toxicity.

In one animal study, rats were exposed to 5,100 mg GBL/m³ for four hours. The animals showed shallow breathing, nasal discharge, lethargy, and limb disuse. All animals recovered however completely in the following fourteen-day observation period.

Rats and mice given a single intraperitoneal injection of GBL showed inactivity in movement, lowered body temperature and cataleptic effects. These effects started to occur at doses of 50 mg/kg bw and higher. A few hours after administration the effects disappeared completely.

Animal studies have been performed, in which rats and mice received different doses of GBL by gavage during two weeks, thirteen weeks, and two years. The main treatment-related effects observed were lowered body weight and death at the highest dose given, and lowered activity combined with irregular breathing. The latter effects started to occur at 225 mg/kg bw and higher. The investigators reported that in the first two to three weeks the lowered activity and irregular breathing were observed within a few minutes after administration, and then completely disappeared after a few hours. In the following weeks no such effects were observed at all, even not directly after administration, suggesting that some form of adaptation or tolerance has occurred. Animals, which were dosed 175 mg GBL/kg bw or lower did not show treatment-related effects during the whole experimental period.

Animal research did not reveal clear evidence for carcinogenicity after oral and dermal exposure in rats or mice. In one study, a slight increase in medullary hyperplasia in adrenal glands was observed in a low dose group with male mice (262 mg/kg bw); in the highest dose group with male mice (525 mg/kg bw) mortality was increased, as a consequence of which the sensitivity of the study to detect carcinogenic effects was reduced. In that study, no evidence for carcinogenicity was noted in female mice at either of the doses tested, nor in both sexes of rats.

Some studies have been performed to assess whether GBL was able to damage genetic material. The available data were negative, although it cannot be excluded with certainty that GBL is able to damage chromosomes in *in vitro* tests.

Finally, animal studies have been published on the reproductive toxicity of γ -butyrolactone. There are indications that GBL reduces the fertility in female rats given intraperitoneal injections of 62 mg/kg bw. However, more research is needed before the relevance of the finding for humans can be made. It is furthermore unclear whether GBL can affect progeny, because data are lacking, and data which are available are of insufficient quality.

Evaluation and recommendation

From the foregoing, the DECOS considers the adverse effects on the central nervous system (CNS) the most critical effects caused by exposure to γ -butyrolac-

tone (and its metabolite γ -hydroxybutyrate). Furthermore, from the data, the committee deduces that workers can experience CNS effects that can affect negatively the alertness of the worker within a few minutes after inhalation. To protect against such acute effects, a health-based recommended occupational exposure limit (HBR-OEL) is needed for short-term exposure. Therefore, the DECOS has assessed whether an HBR-OEL can be derived, as a 15-minute time weighted average concentration (15-min TWA HBR-OEL).

There are no data on humans exposed by GBL or GHB by inhalation, but there are data on single oral intake of both compounds. From these data, the DECOS concludes that CNS effects still occur at doses of 20 mg GBL/kg bw and 10 mg GHB/kg bw; data on lower doses are not reported. When GBL is absorbed from the gut, it is very rapidly metabolized to GHB. Therefore, the DECOS finds it justified to use data on GHB, and uses the dose of 10 mg/kg bw as starting point in deriving an HBR-OEL. This dose is corrected with a factor of 3 for the absence of a no effect level, and an additional factor of 3 to take into account for inter-individual differences. Applying these factors, a oral dose of 1 mg/kg bw is derived.

Because an HBR-OEL concerns *inhalation* exposure and not oral exposure, the dose should be extrapolated to a concentration of the substance in the air. For that purpose data on oral and inhalation bioavailability are needed. Since data on oral bioavailability of GBL are not available, the committee has used data on GHB. The oral bioavailability of GHB is reported to be 27%. Assuming, furthermore, an inhalation bioavailability of 100%, and that a worker weights on average 70 kg, and inhales a volume of 0.3 m³ air during a working period of 15 minutes, the DECOS derives an HBR-OEL for γ -butyrolactone of 65 mg/m³, as a 15-min TWA concentration.

The committee notes that in case of continuous exposure of subsequent 15-minute periods to 65 mg/m³, at the end of an 8-hour during working day, accumulation of GHB in the body may have occurred. This is due to the fact that the time the body needs to eliminate the substances completely is longer than 15 minutes (plasma half-life values of GHB ranges between 30 and 60 minutes).^{*} This means that the internal dose can rise above the internal dose after a single 15-minute exposure to 65 mg/m³, and that a worker may experience CNS effects. Therefore, to prevent this from happening, an 8-hour TWA HBR-OEL is required. This 8-hour TWA should also protect against harmful CNS effects found in humans after long-term exposure.

* In the Netherlands, in principle no legally binding limitation applies for the number of times that a 15-minute TWA OEL may be reached during a normal working day, under the condition that the 8-hour TWA OEL is not exceeded.

No exposure data on long-term exposure levels in humans are available, but there are some data from (sub)chronic animal studies. These studies, in which GBL was given orally for up to two years, hardly showed adverse health effects; the only clear observation was a decrease in body weight. At the beginning, the animals showed slight inactivity directly after GBL administration, but this phenomenon disappeared completely after a few weeks in study. Taking all the available data on long-term exposure into account, the DECOS is of the opinion that these are insufficient to derive an 8-hour TWA HBR-OEL. However, the 15-min TWA HBR-OEL in combination with data on plasma-half lives of GHB allow an assessment of an 8-hour TWA.

Using the plasma half-life of 60 minutes, and assuming that *every* 15 minutes the 15-minute HBR-OEL conditions apply, at the end of an 8-hour working day the internal dose accumulates by a factor 6.5 compared to the internal dose after a single exposure to the 15-minute TWA HBR-OEL. To prevent that accumulation is too high at the end of the day, the 15-minute HBR-OEL is divided by the 'accumulation' factor. This results in a health-based recommended occupational exposure level for γ -butyrolactone of 10 mg/m³, as an 8-hour time weighted average concentration.

Health-based recommended occupational exposure limit

The DECOS of the Health Council recommends a health-based occupational exposure limit for exposure to γ -butyrolactone of 65 mg/m³, as a 15-min TWA, and of 10 mg/m³, as an 8-hour TWA.

Contributing to innovation and the knowledge infrastructure

Synthetic biology: creating opportunities

Health Council of the Netherlands, Advisory Council on Health Research, and Royal Netherlands Academy of Arts and Sciences. Synthetic biology: creating opportunities. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/19. ISBN: 978-90-5549-742-3 (in Dutch and English)

Synthetic biology

Synthetic biology is the engineering of biology: the synthesis of complex, biologically based (or inspired) systems, which display functions that do not exist in nature. This engineering perspective may be added at all levels of the hierarchy of biological structures – from individual molecules to whole cells, tissues and organisms. In essence, synthetic biology will enable the design of “biological systems” in a rational and systematic way. The Committee has used this European consensus definition of synthetic biology in this advisory report. The Committee considers synthetic biology an innovative approach in the life sciences with potential significance for science and society. The advisory report addresses the questions posed by the minister of Education, Culture and Science.

Current status in the Netherlands

Currently, internationally prominent initiatives in this field of research are being developed in the Netherlands. Dutch research focuses on two main directions, both of which have accumulated a large body of expertise over time. One involves metabolic reprogramming of biological systems (*in vivo*, top-down approach) and the other bio-nano-science (*in vitro* approach).

Developments in synthetic biology

Developments in synthetic biology can be classified both by the degree of complexity and by the degree of divergence from nature. Metabolic reprogramming involves experimental systems with a high level of complexity and low divergence from nature. The experimental systems used in bio-nano-science are less complex but are very different from what exists in nature. To date synthetic biology has not yet enabled the construction of fully artificial systems with a high degree of complexity. In fact, many researchers doubt whether it will ever be possible to construct a fully synthetic organism, representative of the highest degree both of complexity and divergence from nature.

Possible significance of synthetic biology

Despite the uncertainties surrounding future developments, synthetic biology is clearly a promising and innovative research area, with potential applications for society. Products arising from synthetic biology can benefit people's health and their quality of life, make medications cheaper and more accessible, and enhance the sustainability of society. In the field of health and quality of life, such products may include live therapeutic agents, biology-based drug delivery systems and sophisticated diagnostic agents. More efficient production platforms could make medicines cheaper and thus more accessible. In the field of sustainability, synthetic biology is focusing on sustainable bio-fuels. Apart from the above applications, which have a direct and tangible impact on people and society, synthetic biology can be applied in areas such as new materials and the establishment of production platforms for fine chemicals. All these potential applications are of interest to the biotechnology industry. For researchers investment in synthetic biology offers the opportunity to successfully compete with the international research community in this field.

Whether synthetic biology can live up to these promises depends on a number of factors. Some of these are external factors which are difficult to influence but which can boost or cut demand for specific products. One example is the combination of decreasing fossil fuel supplies, high oil prices, fears about climate change, and rising demand for food and agricultural land. This generates a need for sustainable production of bio-fuels that does not interfere with food supply. The second factor that will determine the success of synthetic biology is the extent to which society accepts this technology. It is essential to provide people with accurate and balanced information, in order to avoid disproportionate public concern and to curb unrealistic expectations. Similarly, it is important to take

society's concerns into account, in order to establish and maintain confidence in this technology.

Legislation and risk control

The Netherlands Commission on Genetic Modification (COGEM) will advise the minister of Housing, Spatial Planning and the Environment (VROM) on legislation and risk control concerning synthetic biology. Furthermore, the working group *biosecurity* of the KNAW has formulated general rules of conduct.

Recommendations

Synthetic biology offers opportunities to the Dutch knowledge economy, while universities are expanding their existing infrastructure in this area. Therefore, it would make sense for the government to invest in this area of research. Such investment in synthetic biology by the government could very well relate to existing initiatives or plans, such as the Netherlands Genomics Initiative, NanoNed, and the Systems Biology Programme to be launched by the Netherlands Organisation for Scientific Research (NWO). Accordingly, an obvious approach would be to incorporate a sub-programme for synthetic biology into each of these initiatives. Secondly, given the special nature of synthetic biology, it is important to invest in interdisciplinary research and to adapt relevant Master's degree programmes to these new developments. Thirdly, there should be a substantial focus on research into, and communication about, the societal aspects of synthetic biology. The Committee also recommends to, after a given period of time (e.g. five years), survey the Dutch research in the field of synthetic biology in order to assess the need for targeted incentives.

Securing the data supply

Advisory Council on Health Research. Securing the data supply. The availability of population health information in the Netherlands, now and in the future. The Hague: Health Council of the Netherlands, 2008; RGO no. 58. ISBN: 978-90-5549-730-0 (in Dutch)

Effective public health policy and productive scientific research both depend on the availability of data on population health in the Netherlands. The supply of such data is currently not as good as it might be, however. Furthermore, the data that are available are not always utilised to best effect.

That is, in a nutshell, the background to this report by the Advisory Council on Health Research (Raad voor Gezondheidsonderzoek, RGO). In this report, the Council analyses the requirements for empirical data on the health of the Dutch population. The Council also seeks to clarify the extent to which existing data collections can satisfy these requirements, the shortcomings of such data collections and the steps that should be taken to ensure that existing and future data collections are utilised as efficiently as possible. The report concludes with a number of recommendations regarding ways of ensuring that, in the future, public health policy-makers, the health care sector and the scientific community have access to the data they require.

Data on population health are essential for policy management and scientific research

In order to pursue effective public health policies, the government needs to have information about trends in the prevalence of disease, risk factors, disabilities, care consumption and mortality. Data on the risk factors associated with common

conditions are necessary for various purposes, including the estimation of disease burden and healthy life expectancy in the future.

Furthermore, information about changes in the health of the general population is a prerequisite for scientific research into the causes of disease and aging, and for arriving at an understanding of the reasons for observed trends in population health. Such an understanding is necessary for the formulation of appropriate policies and for their subsequent evaluation.

Appropriate methods for generating the necessary data are already available

For the documentation and study of changes in population health, three methods of data collection are particularly important: (repeated) cross-sectional research, longitudinal epidemiological research and data registration. The repeated study of sufficiently large cross-sections of the general population is a good way of identifying trends in the prevalence of risk factors and disabilities. The prevalences of particular diseases and disabilities can be estimated using data from repeated cross-sectional research and registries. Registries can also yield information about mortality, causes of death and care consumption. Longitudinal epidemiological research – i.e. research in the context of which information is gathered on a given group of people at different points in time – is important mainly to support scientific research, including research designed to explain trends in population health.

Current research activities are unable to provide the data needed for policy management

There is presently no source of up-to-date representative data of a kind that can shed light on trends in important risk factors in the Netherlands, such as high blood pressure and serum cholesterol levels. As a result, the estimates of future disease burden and healthy life expectancy available to policy-makers are increasingly unreliable. The Health Examination Survey 2008 promises to go some way to providing appropriate data. However, it is limited in its scale and its (financial) continuity has yet to be assured. The Netherlands also lacks a robust source of data on trends in the prevalence of disabilities. By contrast, national trends in the prevalence of many diseases and medical conditions can be estimated from health care sector data registries, provided that their continuity is assured. The uncertainty that surrounds the future of the National Registry of

Hospital Admissions (Landelijke Medische Registratie, LMR) illustrates that continuity cannot be taken for granted.

The longitudinal data collections require maintenance

Longitudinal epidemiological data collections are essential for scientific research into the causes and courses of disease, aging and trends in population health. However, their scale and duration, and the quality requirements that the data must meet mean that such collections are expensive. Research groups have for many years found it difficult to maintain the infrastructure needed. If the Netherlands wishes to retain its best researchers, its strong scientific position and its ability to contribute actively to innovation in the care sector, the infrastructure of successful longitudinal epidemiological data collections will have to be secured.

Utilisation of the available data can be improved

For the reasons explained above, the collection of data on population health in the Netherlands needs to be continued and extended. However, it is also important to ensure that the data that *are* available are utilised to best effect. Data utilisation is not presently all that it might be.

The main routes to better data utilisation are as follows:

- Secondary analysis: re-using data to answer questions other than those that originally motivated collection.
- Pooling of data collected in the same way, but by different people in different places. This would have the effect of increasing the number of research participants and therefore the reliability of the research. Internationally, efforts are being made to combine biobanks and to pool other longitudinal epidemiological data collections. Pooling does, however, necessitate harmonised research methods.
- Linkage of data on various events in subjects' lives, which are recorded in different data files. Linking data in the register of causes of death to data on a population cohort provides an example. Linkage requires a 'linkage variable', to ensure that the correct individuals' data are being linked.

Data sharing is necessary, but caution should be exercised

The efficient use of data often depends on the body or research group that has collected the data sharing them with others. That is possible only if the privacy of the data subjects is protected, as required under the applicable legislation and

regulations. However, even when adequate protection can be provided, opportunities for data sharing are not always utilised – partly because of obstacles associated with competition within the scientific community.

The Council takes the view that data generated using public resources* should be available for research that is of public value, even if conducted by researchers unconnected to the original data collectors. Nevertheless, the interests of the researchers whose knowledge, skill and effort made the creation of a data file possible must be respected.

Recommendations

In light of the considerations described above, the RGO makes three recommendations to policy-makers, researchers and research funding bodies.

1 Promote the efficient use of data collections

a *Establish a register of data collections*

The Council recommends the establishment of a register of existing and new data collections in the area of population health, so that everyone can see what data are already held, and by whom.

b *Optimise access to data*

The RGO favours the formulation of a *code of conduct on data sharing*. The Council believes that the Dutch Federation of Biomedical Scientific Societies (FMWV) and/or the Royal Netherlands Academy of Arts and Sciences (KNAW) could play an important role in this context. Research funding bodies can contribute by making their support dependent on satisfaction of the following four conditions:

- Registration of the data collection.
- Subscription to the code of conduct on data sharing.
- The definition, in the funding application, of a procedure for providing outside access to the data.
- The use of validated standard test methods, except where properly justified.

* By 'public resources', the Council means not only public research funds (as provided by the government and health organisations), but also the government resources and premiums/contributions paid into collective schemes, which are invested in the data registration systems operated by, for example, Statistics Netherlands, health insurers and care providers.

c *Maximise the scope for data sharing*

The RGO supports the appeal made to the government by the FMWV and KNAW, to allow the *Citizen Service Number* ('burgerservicenummer', BSN) to be used for scientific research purposes. The linkage of data from various sources would require the involvement of a *trusted third party*: a body that is independent both from the parties that maintain the separate data files and from the parties that make use of the linked data.

d *Facilitate data sharing*

The Council believes that it should be made as easy as possible for researchers to share data. To this end, the Council would like to see the creation of an independent *data broker*, whose role would be to put parties seeking data in touch with parties in possession of data, and to assist the sharing of data. The Council also wishes to see the provision of *practical help and support* with the technical aspects of sharing, pooling and linking data. The Council recommends that research funding bodies make resources available for such facilitative activities.

2 Repair data shortages and prevent the development of new ones

a *Provide for repeated cross-sectional health surveys on an appropriate scale*

The RGO recognises that useful data are generated and collected in significant volumes in the Netherlands. However, from the policy viewpoint, there is one clear shortcoming: no repeated cross-sectional surveys are carried out on a scale sufficient to provide a periodically updated picture of the prevalences of risk factors and disabilities. The Council accordingly recommends the establishment in the Netherlands of a programme modelled on the US National Health and Nutrition Examination Survey (NHANES). If policy is to take account of the health status of particular population groups, such as ethnic minorities, these groups must be properly represented in the research undertaken.

b *Ensure the continuity of systems for recording care consumption in hospitals*

The registration of care consumption in hospitals in the LMR serves not only as an important source of information about care consumption, but also as a supplementary source of disease prevalence data. The RGO supports the policy of the Ministry of Health, Welfare and Sports to secure the continuity of the LMR, which is threatened by changes in the way care is organised.

- c *Provide adequate funding for longitudinal epidemiological data collections*
Longitudinal epidemiological data collections are vital for scientific research into health. Without them, it is impossible to explain trends in population health. The RGO regards such data collections as serving an important public need and accordingly wishes to see systematic funding for those that are actively utilised and scientifically successful. The implementation of this recommendation would require coordinated action by research funding bodies such as the Netherlands Organisation for Scientific Research (NWO), Netherlands Organisation for Health Research and Development (ZonMw) and the health funds.

The Council believes that the funding of longitudinal data collections should depend on successful utilisation of the data. New users of the data could contribute to the maintenance of the collection they use by including in their funding application, as a *separate cost item*, provision for a generous contribution to the cost of the infrastructure that supports the collection. Of course, this requires that research funding bodies are willing to contribute in this way to the continuation of successful data collections.

3 Give more room to applications for the public funding of new data collections and assess them systematically

Even if existing data are put to optimal use (recommendation 1) and identifiable (existing and potential) blind spots are addressed (recommendation 2), the RGO believes that there will remain a need for initiatives designed to provide as yet unavailable data required by researchers and public health policy-makers. However, finite public resources need to be used efficiently, even if only to maximise the number of innovative ideas that are supported. The Council accordingly recommends that all applications for the public funding of new data collections should be assessed on the basis of a number of requirements relating to relevance, necessity, quality and efficiency. A proposed assessment framework is set out in the box below. Applications for the funding of new rounds of data collection within ongoing studies could be assessed on the basis of the same requirements.

The RGO expects that, together, these three recommendations will contribute to ensuring that in the Netherlands, in the future, the data necessary for effective public health policy and high-quality scientific health research are available.

Framework for the assessment of applications for the public funding of new public health data collections

Are the data to be collected relevant?

The proposed data collection:

- 1a is scientifically relevant, in the light of the scientific status quo and/or
- 1b meets a policy need.

Is the new data collection necessary?

The purpose to be served by the proposed data collection cannot be met adequately by:

- 2 an existing or current data collection in the Netherlands;
- 3 an existing or current data collection outside the Netherlands;
- 4 the combination or linkage of existing data in the Netherlands;
- 5 the combination or linkage of existing data outside the Netherlands; or
- 6 supplementary data collection within the context of an existing data collection system.

Will the new data collection satisfy the quality and efficiency requirements?

- 7 The proposed data collection satisfies the applicable quality requirements.*
- 8 The proposed data collection model is the most cost-effective option.
- 9 The cost of the new data collection will be justified by the benefit.**
- 10 The proposed model meets the criteria for funding proposed by the RGO to promote data sharing.***

* Applicable quality requirements include the following: the proposed research model must be capable of providing answers to the scientific questions addressed; the proposed research model must be consistent with the (inter)national scientific status quo; the proposed research model must provide scope for control, e.g. in the forms of audits. **The benefit of a new data collection may derive not only from its direct scientific or policy relevance, but also from, for example, the added value attainable by combination or linkage of the collected data with existing data, or from the expectation that the collected data will enable future scientific questions to be addressed. *** See recommendation 1b in this summary.

Healthy services research

Advisory Council on Health Research. Healthy services research. The future of health services research in The Netherlands. The Hague: Health Council of the Netherlands, 2008; RGO no. 59. ISBN: 978-90-5549-736-2 (in Dutch)

Background

In response to questions from the Lower House of Parliament about the knowledge infrastructure for health sciences the Minister of Health, Welfare and Sport has identified the need for an analysis by the Advisory Council on Health Research (RGO). The minister formulated two central questions: ‘... whether the knowledge infrastructure is of sufficient size and stability to properly address the questions regarding developments in the health care system now and in the future’ and ‘... whether there is a good balance between free risky innovative research and request guided research’. For both questions he requested ‘... a good analysis and a convincing answer’ by the RGO.

Health services research in this advisory document

Health services research addresses the structure, organisation, functioning and effects of health services, and the ways in which these interact with demand for, and use of, these health services. Health services research covers the whole field of health care, i.e. cure, care and preventive healthcare.

Health services research supports the societal tasks

In 2006 the Ministry of Health, Welfare and Sport formulated the Societal Tasks as a guiding principle for the knowledge and innovation agenda of the health care sector. These tasks have recently been updated and are as follows:

- 1 Anticipating a growing and changing demand for healthcare
- 2 Living longer in good health and participate longer in society
- 3 Quality of care and patient safety
- 4 Governance in health care
- 5 Managing limited healthcare resources (shortages and risks).

Health services research can contribute significantly to each of these tasks. In the report a number of examples are given.

The Netherlands has a good research infrastructure that in part may be improved

Since the previous advice on health services research by the RGO in 1994 a lot has changed for the better. The majority of the research is concentrated in a number of larger institutes, researchers transfer their knowledge in a targeted manner, and the scientific and social quality of the research has increased. The establishment of the Netherlands Organisation for Health Research and Development (ZonMw) has certainly contributed to these developments. The total budget for health services research is – compared to that in other countries – adequate.

However the ratio between direct, indirect and contract funding, and the way of programming health services research at ZonMw need further improvement.

Health services research funding typically involves relatively small amounts of direct (government) funding and relatively large amounts of contract funding. This ratio can be easily explained by the large amounts of commissioned health services research. However, the ratio is now such that the ability of the field to perform 'risky, innovative research' is under pressure. This situation may endanger the stability of the research field, threaten capacity building and decrease responsiveness of the field.

Programming of health services research by ZonMw may be improved by providing less strict frameworks. Thematic programming, as such an excellent manner to create focus and mass within health research, is due to its nature not always suitable for health services research. Strict frameworks within a programme hamper flexible funding of health services research that exceeds specific

themes and prevents researchers to quickly address new questions from policy and practice.

The knowledge infrastructure

For optimal use of health services research and researchers, systematic and mandatory interaction between researchers and knowledge-users at every stage in the knowledge cycle is crucial. This interaction is still rare, which results in suboptimal use of knowledge.

Recommendations

The RGO makes two main recommendations to the Ministry of Health, Welfare and Sport, researchers, research funders and the health care sector.

- 1 Reinforce the research infrastructure in such a way that practical and policy issues can be rapidly addressed, while allowing sufficient scope for innovation on the part of the research community.
 - a *Put in place a broad and flexible programme of health services research*

The shortcomings of the current thematic programming are such that they justify the establishment of a separate ZonMw programme on the theme of health services research. This programme should be based on the knowledge agenda for health services research (recommendation 2a) and should provide for research funding that is sufficiently flexible to afford scope both for addressing ad hoc issues and for developing stable, continuous lines of research.
 - b *Promote well-balanced health services research funding*

A healthy balance between direct, indirect and contract funding will ensure that the necessary innovation capacity is sustained. This healthy balance can be achieved by allocating direct funding in proportion to the power of the research group in question to attract contract funding.
 - c *Promote equitable funding allocation within the ZonMw Open Programme*

Prioritisation within the Open Programme would better reflect the frequently high quality of the research proposals if it were to focus on strengths rather than on the weaknesses: the inherent methodological vul-
-

nerability that inevitably results from the complexity of health services research.

d Create PhD fellowships

PhD fellowships enable junior researchers to enhance theoretical and/or methodological aspects of their research. This effort to enrich the training of young researchers is aimed at guaranteeing high-quality capacity building.

e Stimulate international comparative research

Even though health services research often deals with regional/national issues, international experiences are highly valuable. Therefore, maximally use foreign experiences by stimulating international comparative research.

2 Ensure systematic and mandatory interaction between researchers and knowledge-users in order to improve the exploitation of knowledge

a Formulate the knowledge agenda for health services research interactively

The knowledge agenda should be developed through an interactive exploration. This type of exploration not only serves to identify and prioritise the topics for the knowledge agenda but also provides a platform for systematic interaction between researchers and different groups of knowledge-users (central government, care providers, insurers, patients, municipal authorities, etc.). To flesh out the practical details one can draw on the experiences of organisations such as ZonMw. The knowledge agenda serves as the basis for the broad and flexible public research programme mentioned in recommendation 1a.

b Encourage cooperation between centres of expertise and knowledge-users

Cooperation between centres of expertise and knowledge-users can be further promoted by giving relevant organisations (such as healthcare facilities, insurers and municipalities) a firm place within the knowledge infrastructure through the creation of workplaces for researchers within these organisations.

c Promote implementation and an understanding of success and failure factors

Stipulate that the researchers and knowledge-users jointly draw up an implementation plan for health services research projects in advance and then review the projects afterwards to determine the extent to which the goals described in the plan have been achieved. The scientific foundations for implementation strategies can be laid with the aid of implementation research.

d Make evaluation a formal component of every transition in policy and health care practice

When embarking on new policy or new interventions, provision should be made from the outset for fixed time points for assessment in order to allow for the evaluation of policy and decisions. Both researchers and the institutions directly involved in the new policy or intervention should take part in the evaluation.

e Instruct researchers and knowledge-users about each other's working practices

Open communication and mutual respect between the players in the knowledge cycle can be promoted by instructing researchers about policy and decision-making processes and instructing knowledge-users about how the research process operates.

A Other publications

Annex

Other publications

- Advisory letter High-voltage power lines (2008/04E, in Dutch and English)
 - Advisory letter Air quality and increased risk locations (2008/09, in Dutch)
 - Protocols for social insurance physicians: Whiplash associated disorder, Aspecific low back pain (revision 2008), Myocardial infarction (revision 2008) (2008/09, in Dutch)
 - Advisory letter BioInitiative report (2008/17E, in Dutch and English)
 - Advisory letter Conditions for participation in traffic after a cerebral haemorrhage (2008/20, in Dutch)
 - Advisory letter Assessment framework for food quality (2008/23, in Dutch)
 - Advisory letter Round Table Conference on Q-fever in the Netherlands (2008/28, in Dutch)
 - Annual Report 2007 - Health Council of the Netherlands/Advisory Council on Health Research (A08/01, in Dutch)
 - Health Council of the Netherlands - Reports 2007 (A08/02, in English)
 - Performance and Perspective - Report for international review (A08/03, in English)
 - Maintaining and modernizing- International review and reaction (A08/04E, in Dutch and English)
 - Social Annual Report from the office of the Health Council of the Netherlands/Advisory Council on Health Research 2007 (A08/05, in Dutch)
 - Work Programme 2009 Health Council of the Netherlands (A08/06E, in Dutch and English)
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- Organisation- and Formation Report of the Secretariat of the Health Council of the Netherlands (A08/07, in Dutch)
- Seven honorary members counsel the Council (A08/08, in Dutch)