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...” (Section 21, 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, and Agriculture, Nature Preservation & Fisheries. 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 healthcare to the Dutch Government. 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 drawn up by independent, multidisciplinary committees of experts.

The present volume is a compilation of the executive summaries of reports published in 2003. Copies of all reports, however, can be downloaded from our website: www.healthcouncil.nl. Paper versions can be obtained from

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Participation in sport can lead to physical injury. Brain injury is one of the most serious forms of injury that can occur. In soccer, players can suffer brain injury as a result of others infringing the rules, as a result of ‘accidents’, and possibly as a result of repeated or poorly executed heading of the ball. In boxing, there is an inherent risk of brain injury, since the sport’s ultimate aim is to knock out one’s opponent. Repeated acute brain injuries – concussions, for example – can lead to the development of chronic brain injury, and ultimately to dementia in the most serious cases.

Both in the world of sport and in medical circles, there has for some time been debate concerning ways of preventing sports-related brain injury. After questions on this subject had been raised in parliament, the State Secretary for Health, Welfare and Sport asked the Health Council to prepare an advisory report. In *Brain injury in boxers and soccer players*, a Committee of the Health Council focuses on the problems in the sports of boxing and soccer and addresses the following questions:

- How common is sports-related brain injury and what gradations of injury – both acute and chronic – may be distinguished?
- How can brain injury be detected, and how valuable is neuropsychological testing as a diagnostic tool?
- What can be done to prevent sports-related brain injury?
Incidence of brain injury

Not a great deal is known about the prevalence of brain injury in boxing or other fighting sports. Given that inflicting brain injury is one of the intrinsic aims of boxing in particular, little or no research has been conducted into the prevention of such injuries. No attempt has ever been made to quantify the incidence of acute brain injury in professional boxers. However, studies showed that one in eight amateur contests ends in concussion. Information from the Amateur International Boxing Association (AIBA) indicates that the percentage of contests at world championship and Olympic tournaments stopped because of brain injury has declined in recent decades, from about 10 per cent to no more than 3 per cent. This may indicate a fall in the incidence of concussion at such tournaments, but this possibility has not been investigated. It has been convincingly demonstrated that between 40 and 80 per cent of professional boxers suffer chronic brain injury. The seriousness of the abnormalities appears to be related to the number of bouts. Amateur boxers are also affected by chronic brain injury, but no data on the incidence is available and the evidence suggests that the problem is much less serious than among professional boxers.

With regard to soccer, the most informative research data indicates that there are six cases of concussion in every ten thousand men’s matches/training sessions, and four cases in every ten thousand women’s matches/training sessions. The average player has about a 50 per cent chance of suffering concussion at some point in his/her playing career. There is no evidence to suggest that heading the ball can cause concussion. The Committee knows of only one study reported to date that looked at the subject of chronic brain injury in ex-professional soccer players. Neuropsychological tests indicated that eight of the ten former players participating exhibited abnormalities (albeit mild in some cases). It is not clear to what extent the subjects are comparable with modern-day players, since various aspects of the game have changed over the years. Studies involving active soccer players have produced mixed findings; some have suggested that soccer is associated with chronic brain injury, while others have found no link. Notably, chronic injury has been observed only in players who have executed more than a thousand headers.

The interpretation of data on sports-related brain injuries is complicated by significant inter-study inconsistency in the definition of acute and chronic brain injury. In fact, the findings of the studies reported to date cannot properly be compared. If insight into the incidence of acute and chronic sports-related brain
injuries is to be improved, further and more specific sports-epidemiological research is required.

The detection of brain injury

A preliminary on-the-spot diagnosis is normally required when an incident occurs in order to decide whether the individual in question is fit to continue with the game or contest. In the Netherlands, use is currently made of the symptom classification system set out in the Richtlijnen voor de diagnostiek en behandeling van patiënten met licht schedel-hersenletsel (Guidelines on the Diagnosis and Treatment of People with Slight Cranial Brain Injury), published by the Netherlands Association for Neurology. However, this scoring system is intended for use by physicians and is consequently unsuitable for on-field use by lay people. The Committee therefore recommends adoption of the system developed by the American Academy of Neurology. This system uses clearly defined criteria and is more widely accepted than the other systems currently in use. Furthermore, the associated guidelines on minimising the consequences of acute brain injury lend themselves to application in the Dutch sporting context because of the clear criteria for the resumption of sporting activities.

If chronic brain injury is to be detected as early as possible, anyone suspected of such injury should undergo neurological and neuropsychological testing. In the context of such testing, it is always preferable to compare an individual’s performance against his or her baseline data, rather than group averages. For this reason, the Committee considers it important that athletes should undergo tests as early in their careers as possible, in order to gather baseline data. It is not feasible to organise testing for the great mass of amateur athletes, but it should be possible to test professionals, who are at greater risk because of the time they devote to their chosen sport. In addition, the Committee recommends that neuropsychological testing forms an integral part of compulsory periodic check-ups for participants in sports associated with a high risk of brain injury. This would enable prompt action in cases where an individual’s cognitive functions appeared to be deteriorating. An athlete thus found to be suffering from chronic brain injury should be advised to refrain from all sporting activities that might aggravate the injury. The systematic collection of neuropsychological data regarding athletes would have the added advantage of contributing significantly to scientific knowledge regarding the sensitivity and specificity of neuropsychological testing and thus facilitating their improvement.

Neuropsychological tests are uniquely capable of demonstrating acute brain injury and detecting chronic brain injury at an early stage of development. Such
tests can reveal brain injuries at an earlier stage than is possible using imaging techniques. The use of neuropsychological tests is also preferable to the use of serum markers, which currently have little practical value in the detection of acute sports-related brain injuries. However, if the sensitivity and specificity of serum markers as indicators of brain injury should ever be demonstrated, and if a kit were to become available, with which plasma levels could be determined on the spot, serum markers could perhaps be used for this purpose in the future.

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**The value of protective headgear**

Helmets have been proven to be effective in the protection against acute brain injury. It is as yet unknown whether they also protect against chronic injury, but it is likely that reducing the risk for acute damage will have a preventive effect on long-term effects.

The head cap worn by amateurs in boxing and other fighting sports mainly prevents superficial injuries to the head. The forces acting upon the head are absorbed only to a limited amount. Such headgear offers insufficient protection to boxers’ brains.

Studies into the effectiveness of protective headgear for soccer players have given mixed results. These devices also protect against superficial injuries, but protection against brain damage is doubtful.

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**The prevention of brain injury in boxing**

Boxing inflicts health damage. It is the question whether the extent and severity of this damage justifies that the authorities interfere with the autonomy of the fighters and to impose limitations to boxing or even a ban. The Committee feels that this is indeed the case, specifically for professional boxing.

Professional boxing entails a great deal more risk than amateur boxing because no head protection is used and the bouts are longer; in addition, professional boxers generally spar more often and for longer. As a result, a professional boxer is at great risk of chronic brain injury. Furthermore, the sometimes-considerable financial incentives to win can induce a boxer to accept higher risks. These problems are exacerbated by the fact that the Dutch Boxing Association makes little or no provision for the medical supervision of professional boxers. The Committee believes that rule changes are required to reduce the risks associated with professional boxing. If it should not be possible to implement appropriate rule changes within a reasonable space of time, or if it should be concluded that rule changes are unlikely to have any significant effect...
on the occurrence of brain injury, the Committee strongly recommends the prohibition of professional boxing in the Netherlands. In various countries where professional boxing has been banned for some time, the experience has been that this does not give rise to practical problems. Consideration should also be given to outlawing participation in other fighting sports whose rules permit the infliction of brain injury. One option would be to make prohibition temporary, pending the development of suitable measures to minimise the risk of injury.

All people participating in boxing and other fighting sports should be fully informed about the short-term and long-term health risks associated with participation. No one should be allowed to participate competitively without first being made aware of and accepting the risks (i.e. participation only on the basis of informed consent). The Committee strongly recommends that young people under the age of sixteen should not be allowed to compete in boxing or other fighting sports that can inflict brain injury.

The annual physical examination that boxers are required to undergo should be made more rigorous; it should be made compulsory for all boxers – including non-competitive boxers – and all fighting sport participants, and it should include neuropsychological testing. Competitive boxers should also be examined using imaging and electrophysiological techniques. In the event of cognitive disorders being detected, the subject should be strongly advised to refrain from all sporting activities that involve a risk of brain injury. Where possible (where there is a supervisory medical committee), the person in question should be barred from participation in boxing and fighting sports for life.

If a boxer loses a bout following a KOH (knockout – head) or an RSC-H (referee stopping contest – head), he or she should undergo neuropsychological testing and neurological examination. The boxer should be suspended from competition until the symptoms of acute brain injury abate.

The Committee wishes to see adoption in the Netherlands of the comprehensive requirements made by the AIBA concerning the training of ringside physicians. Ringside physicians, referees and coaches should also receive regular refresher training.

A physician is bound by the Hippocratic oath to adhere to the principle of ‘beneficence’ (doing and promoting good). The physician therefore faces a dilemma in relation to boxing. Given the physician’s commitment to the principle of beneficence, one may reasonably ask whether it is right for a physician to act as a ringside doctor at a boxing contest or other such event. On the other hand, allowing participants to fight without adequate medical supervision might be regarded as an abdication of responsibility.
Dutch Boxing Association therefore prohibit a contest from taking place without a ringside physician. The Netherlands Association of Sports Medicine (ASM) has issued a guideline regarding boxing and other fighting sports: physicians should endeavour to establish preventive measures and by no means promote these sports activities. The Royal Dutch Medical Association has ruled that all physicians in the Netherlands are to observe the ASM guidelines.

### The prevention of brain injury in soccer

Whenever brain injury is suspected, the Committee would like to see the guidelines developed by the American Academy of Neurology applied. The additional and more specific advice given by the International Conference on Concussion in Sports ought to be followed in the Dutch sports setting because of the detailed step-by-step plan for a sportsperson’s return to play following a brain injury. Appropriate care following brain injury can prevent aggravation of the damage.

On-site provision should be made for the medical treatment of acute brain injury. Such provision is already made for all professional matches in the Netherlands. The medical personnel in attendance are all given instructions by the Royal Netherlands Football Association on how to respond in the event of a (suspected) brain injury. The Committee believes that compliance with these instructions should be mandatory. Amateur matches are too numerous to make the universal attendance of trained medical personnel practical. In the United States, an easy-to-use reference card has been developed, which lists signs and symptoms of concussion and sets out a number of simple but validated on-the-spot tests that can be used to assess the condition of someone who has received a blow to the head. The Committee recommends the development of a Dutch version of this reference card for on-field use in both professional and amateur sport. All referees and coaches should then be instructed, at least at the beginning of each season, in the use of the card. Wherever doubt exists regarding a player’s fitness to continue following an incident, he or she should be withdrawn from the match and referred for medical examination. The Committee also recommends that professional players should undergo both an immediate on-field test, plus more thorough subsequent testing.

In the interests of brain injury prevention, strict enforcement of the rules of the game is also important. As well as advocating such enforcement, the Committee would like to see the rules modified in two respects. The FIFA is already seeking to outlaw use of the elbow when jumping to head the ball. The Committee’s view is that use of an elbow should be outlawed in all phases of
play as a matter of urgency. In addition, the Committee recommends that a team should be permitted to temporarily substitute an injured player to allow for more thorough examination off the pitch. This would enable a team to give an injured player proper attention without fear of weakening the team’s position in the game.

The Committee believes that players should be instructed in appropriate heading techniques. The effect that heading has on the brain increases as the ratio between the mass of the player’s head and the mass of the ball decreases. This implies that increasing the mass used in heading by tensing the muscles of the neck can reduce the risk of brain injury. Since the head-ball mass ratio is much lower in junior players than it is in adults, the risk of brain injury in children is higher. The Committee therefore supports the Dutch FA’s view that players under the age of sixteen should not be trained to head the ball. The scarce data on possible chronic brain injury as a result of frequent heading is not equivocal. The Committee therefore presently does not believe that there are grounds for imposing other limitations to heading, or for recommending the use of protective headgear by soccer players. Further research is required, however, into the biomechanics of heading; there is a need to add to the existing knowledge in order to facilitate the possible development of protective gear.

It has been suggested that soccer players should wear mouthguards, which are already used in various other sports. However, the Committee does not feel inclined to recommend the use of mouthguards until there is evidence that they would actually be effective in soccer.

Concluding remarks

The Committee would like to see the creation of a knowledge centre to register brain injuries and to coordinate research into the effectiveness of preventive measures, not only for boxing and soccer, but for all sports which may result in brain injuries. The centre could also organise seminars and training courses for sports physicians, coaches and youth leaders. In this way, people in the sporting world could be provided with greater insight into brain injuries and taught what to do in the event of an incident that might involve such an injury. The seminars might vary from introductory outlines for amateur coaches to detailed explorations of the relevant issues for professionals such as sports physicians.
Hematopoietic stem cells

Blood contains various types of cells that develop from hematopoietic stem cells. Diseases can give rise to a deficiency of blood cells, which can sometimes be remedied using stem cells from donors.

Potential sources of these stem cells are bone marrow, blood collected from donors stimulated with substances that “mobilise” the stem cells (mobilised blood), and umbilical cord blood. Recent research findings suggest that hematopoietic and other stem cells may have the potential to develop not only into blood cells but also into other cell types, such as liver or muscle cells. In the long term, these possibilities may pave the way for new clinical applications and thereby alleviate the shortage of organ donors. A great deal of research is still needed, however, before these possibilities can be realised.

In present-day practice, hematopoietic stem cells are primarily used in the treatment of malignant blood diseases such as the leukemias and lymphomas. They also find application in patients with solid tumors such as breast cancer, hematopoietic disorders such as thalassemia and a number of metabolic diseases. A distinction is drawn between autologous transplantations, where the cells are collected from the patients themselves, and allogeneic transplantations, in which case the cells are harvested from a donor.

In applications of this kind, mobilised blood is increasingly taking over the role formerly played by bone marrow, the classic source of stem cells. The collection of bone marrow is more stressful for the donors than the harvesting of mobilised blood, whereas the latter can yield equally good clinical results. The
safety of the procedure deserves careful attention, also in case of mobilised blood donors. Increased use is also being made of umbilical cord blood, though the relatively small number of stem cells collected per donation is a limiting factor. It is therefore important that researchers should explore the possibility of obtaining larger quantities in the laboratory by means of cell division. The development of methods to expand the number of stem cells, regardless the source, may alleviate the shortage of donors. By that shortage, a suitable (tissue-matched) donor is not available for a rather large number of patients, especially migrants.

Another way of alleviating the donor shortage could be to store larger quantities of cord blood for general use via a cord blood bank. Storage for possible autologous use is impractical, however, since the likelihood of such use actually taking place is remote (less than 1:10,000).

Alongside the shift from bone marrow to mobilised blood and, to a lesser extent, umbilical cord blood, there have also been developments with regard to the selection of donors and in treatment techniques. The selection of donors can be improved with the aid of new laboratory tests (molecular typing), which allow large numbers of donors to be matched to suitable transplantees. Furthermore, increasing use is being made of therapeutic methods that partially spare the bone marrow. As a result, the mortality and morbidity associated with stem cell transplantations have declined.

The number of transplantations performed world-wide has fallen in recent years. Less use is made of autologous cells than a few years ago, mainly due to disappointing results in patients with solid tumors. However based on recent results in a certain group of breast cancer patients, an increase is to be expected over the coming years.

The use of allogeneic cells remains virtually unchanged. This fall in the number of stem-cell transplants is expected to be partially offset by an increase in allogeneic stem-cell transplants, prompted by a broader interpretation of the indication for intervention. Partly as a result of the donor shortage, however, there is unlikely to be any substantial increase in the overall total in the near future. No such rise can be anticipated either in the number of transplants in children. Consequently, the current number of centres at which stem-cell transplantations are performed is considered to be adequate for the time being.

Legislation of the donation of stem cells is spread over different laws. However, the mandatory rights and the protection of donors are warranted sufficiently. Also the safety and quality of the stem cells to be used are guaranteed legally in a sufficient manner. The same applies to the quality of the institutions concerned and the expertise of the professionals involved.
Warrants are less well regulated in case of autologous donations. In practice, this situation does not seem to yield problems. Attention should be paid to the quality of the information given to people who consider to store cord blood for autologous use in the future.

The immune system plays an important role in allogeneic stem-cell transplants. Since allogeneic cells are foreign to the body, they can provoke severe immune responses (graft-versus-host disease). Conversely, the allogeneic cells can trigger a significant therapeutic response in tumors (graft-versus-tumor effect). Immunological expertise is therefore indispensable when performing allogeneic stem-cell transplants. Research into the immunological aspects of stem-cell transplants is thus also desirable, as is research into the above-mentioned proliferation of stem cells by means of cell division.

The Committee makes the following recommendations:
• Research into the cell division of hematopoietic stem cells is to be promoted with a view to overcoming the shortage of stem cells for transplantation purposes.
• Research into the immunological aspects of stem cell transplantation is to be encouraged, in view of the importance of graft-versus-host disease and graft-versus-tumor effect.
• Donation of umbilical cord blood for general therapeutic use is to be promoted and storage for autologous use is to be discouraged (in consideration of the shortages and given that autologous use is very unlikely).
• The number centres for allogeneic stem cell transplantation is not to be extended in view of trends in the numbers of those transplantations.
As part of the planned reform of the health insurance system, the Minister of Health, Welfare and Sport has requested the Health Council to “formulate an opinion with regard to the workable, scientifically based criteria for identifying which health care services should be included in a basic package”. The Committee on Contours of the Basic Health Benefit Package gives an account of its findings in this advisory report. To begin with, it outlines the interpretation of governmental responsibility for public health and health care customarily adopted in the Netherlands. Then it examines the considerations that can play a role in decisions regarding the scope and composition of a so-called ‘basic package’. These include: equal access, protection of individuals against themselves, and cost control. Partly on the basis of an international overview of analyses for decision-making on rationing issues, the Committee then specifies the criteria that are relevant when formulating a basic package and investigates the applicability of these criteria.

The Committee’s conclusions and recommendations can be summarized in a number of key points.

**Distinction between solidarity and compulsory insurance**

Criteria for the formulation of the basic package must be derived from the two objectives that such a package seeks to achieve.
First, health care must be readily accessible to all. A ‘solidary’ insurance package is funded on the basis of solidarity of rich with poor, young with old, and healthy with sick. It includes all of the care services for which mutual solidarity can reasonably be invoked. This first objective requires criteria for a ‘solidary’ package.

Second, government should protect its citizens against their own ill-advised decisions and those of others. This objective requires criteria for a ‘compulsory’ package.

Criteria for a solidary package

For which services are people willing to exercise solidarity with one another?

Based on an analysis of earlier attempts (at home and abroad) to develop effective criteria in this regard, the Committee considers that, in theory, individual ‘burden of disease’ combined with ‘cost-effectiveness’ forms a good basis upon which to define a basic package that, in accordance with the principle of solidarity, is accessible to all. Burden of disease is defined as ‘reduced quality of life or life span as a result of a disease or some other somatic or mental health problem in cases where no health care service would be utilized’. The term cost-effectiveness denotes the relationship between the effectiveness of a health care service (i.e., the degree of reduction in burden of disease) and the costs (in terms of financial resources, manpower, equipment and time). Thanks in part to the major advances made in scientific research in recent years, ‘burden of disease’ and ‘cost-effectiveness’ are, in theory, workable criteria that have in the meantime also been applied in a number of situations. However, we currently still lack the data needed in order to apply these criteria to many care services.

Criteria for a compulsory package

For which services is compulsory insurance justifiable?

Burden of disease and cost-effectiveness are not sufficient conditions for this. Additional reasons are required. One can decide on paternalistic grounds to protect individuals against self-made decisions that may prove to have adverse consequences in the longer term. An example of this would be failure to take out insurance for an expensive service that one would not expect to need. Another motivation for compulsory insurance is to protect individuals against unfavourable decisions made by others – for example, if these other parties fail to insure against prevention and care of infectious diseases. A third reason is to
safeguard against the phenomenon of ‘free riding’. Sometimes, individuals seek to pass costs on to other insured persons – for example by forgoing insurance in the hope that, in due course, others will shoulder the costs in a spirit of solidarity. A fourth (and final) possible motive is the desire to promote the efficiency of health care as a whole (‘macro-efficiency’) by introducing compulsory insurance for certain services. An example of this would be the introduction of compulsory insurance for general-practitioner care in order to make proper use of the general practitioner’s gatekeeping function in relation to costly secondary-care services. The following criteria for compulsory insurance can be derived from the reasons cited above:

- the costs of treatment, nursing or care (possibly in relation to the insured’s income position)
- the extent to which the disorder that is to be prevented or treated may afflict other people, or could severely inconvenience them
- the preventive nature of services
- the impact that the use of services has on the efficiency of health care as a whole.

Composition of the package

The two sets of criteria may result in a single basic package, but a ‘solidary’ and a ‘compulsory’ basic package need not necessarily coincide. Based on the analytical distinction drawn by the Committee, it is, in principle, feasible to identify a smaller ‘compulsory’ package within the ‘solidary’ package. Other considerations that the Committee is not fully able to assess – such as actuarial feasibility – may have a bearing on the decisions ultimately reached by the government with regard to the choice between one or two packages.

A national assessment framework

In order to apply the criteria to different services, it is necessary to have a ‘national assessment framework’ that supports rationing decisions. Such a framework is helpful when assessing existing and new services in terms of disease burden and cost-effectiveness, while safeguarding scientific and societal interests. No such assessment framework is currently available, but certain of its elements can be found within several organizations. The national assessment framework will need to accommodate procedures for defining the package, since application of the criteria always requires a qualified approach. Any service or
category of services will have various elements that require careful discussion and evaluation. Examples are: the need to differentiate between the concepts of health and disease, and the multidimensional nature of burden of disease and its reduction (effectiveness). Other considerations of a societal, legal or ethical nature also need to be included in the evaluation. Decision-making can only partly be based on scientific principles, since societal views also have a role to play. This is illustrated by the question of where one should place a threshold in relation to burden of disease. Moreover, at what point do the costs of a service become unacceptably high compared with its benefits? According to the Committee, the establishment of these limit values or thresholds is a task for government, which then requests the administrators of the national assessment framework to assess services in the light of these limit values for burden of disease or efficiency. The Committee recommends that a national assessment framework should be established, taking advantage of the experiences that have now been gathered in the UK with the National Institute for Clinical Excellence (NICE).

Research recommendations

Further research is needed before the basic package can be formulated entirely in the manner that has been proposed above.

First of all, the criteria for solidarity and compulsory insurance will need to be even more clearly operationalized in relation to a number of points.

Second, more research is required in cases where data on individual disease burden or cost-effectiveness are either missing or incomplete. This is particularly important in the case of services that are associated with a large total disease burden and a correspondingly great demand for care among the population, whereas cost-effectiveness is still insufficient or else unknown.

Third, there is a need for research that contributes to effective decision-making on rationing issues.

Finally, further research is needed into means of promoting efficient practices among caregivers.
Introduction

In the early days of kidney transplantation, during the fifties and sixties, donor organs were initially obtained from both living donors and patients who died of a cardiac and circulatory arrest (the so-called ‘non-heart-beating donor’ - NHBD). At that time these were the only suitable organ donors available. This changed when brain death criteria were introduced around 1968, which meant that patients in whom cerebral death was diagnosed could also be considered as potential organ donors. After 1970 the use of these ‘heart-beating donors’ (HBD) became predominant. This trend is also closely linked to the development of effective immunosuppressive drugs and the progressing understanding of the importance of HLA compatibility between donor and recipient, through which the results of cadaveric donation and transplantation have improved substantially.

In this way the number of kidney transplants could be expanded considerably, and this also allowed the transplantation of other organs (e.g. heart, liver and lungs). Furthermore, the successful development of effective organ preservation methods made it possible to transport donor organs over longer distances, and in this way laid the foundation for international organ exchange organizations, such as Eurotransplant and Scandia-transplant.

In the past decades the number of organ donations and transplants in the Netherlands has been massively outstripped by the ever-increasing number of
patients on the transplant waiting list. For almost every type of organ there now exists a substantial waiting list. Also, for all organs the average waiting time till transplantation is on the increase. For instance, in 2003, the average wait for a kidney transplant was well over 1100 days, counting from the first day of dialysis treatment (which equals registration on the waiting list). The proportion of kidney patients on the waiting list being transplanted within a two-year period, has dropped since 1998 from half to less than one-third. Another result of this shortage of donor organs is the substantial mortality on the waiting list, in particular among patients waiting for a heart, liver, or lung transplant.

In all fairness one has to observe that, in the past twenty years, there has been no substantial increase in the number of cadaveric kidney transplants. This number is now around 370 per year, and shows no upward trend. The main cause for this is the gradual, and — so it appears — structural decline of the number of patients from whom organs could be retrieved following determination of brain death. Both the reduction of the number of fatal traffic accidents and the high incidence of family refusals to donate are responsible for this. One cannot but conclude that the actual development of cadaveric organ donation in the Netherlands is reason for serious concern, despite recent efforts at improvement.

These circumstances force one to consider alternative sources of donor organs besides the usual brain-dead cadaveric donor. The Minister of Health, Welfare and Sports in the Netherlands has therefore requested the Dutch Health Council to report on any available alternative sources of donor organs, and to focus in particular on living donor transplants and non-heart-beating donation. This advisory report, which has been drawn up by an expert committee of the Health Council, covers not only the medical state of the art, but also the ethical, legal and social aspects of organ donation.

Renewed interest in living donor transplantation and NHB-donation

The gradual decline in the number of cadaveric donations from heart-beating donors appears to have been partly compensated for by an increase in the number of donations from living donors and non-heart-beating donors. For the time being, this only relates to kidney transplantation. The revival of interest in the Netherlands for these types of donation has resulted in a situation where, in 2003, over 30 percent of all cadaveric donor kidneys originated from NHB-donors. In that same year, one third of all kidney transplants in the Netherlands (a total of 560) have been performed using organs from living donors.

All this justifies the conclusion that the kidney transplant program in the Netherlands is becoming more and more dependent on these ‘novel’ types of
donation, in order to give patients a reasonable chance of getting transplanted. It is therefore imperative that, together with active promotion of heart-beating donation, effective measures are taken to stimulate these types of donation.

**Living donor kidney transplantation**

Kidney grafting using organs from living donors is in fact as old as transplantation itself. The first successful kidney transplant, in 1954, was performed with a kidney from an identical twin-brother. Justification for living donation has, up to now, rested mainly on the degree of blood relationship between donor and recipient. For medical as well as ethical reasons, it has long been assumed that living donation could only take place between persons sharing a close genetic relationship, that is: siblings or parents and children.

During the mid-nineties this view changed. Research has now shown that even kidney donations and transplants between genetically unrelated donor and recipient combinations give good results. This concerns mainly donations between spouses or unmarried partners, but also between in-laws and friends (so-called ‘emotionally related’ donors). These unrelated transplants are comparable in graft survival to transplants involving haplo-identical relatives (e.g. a parent or a sibling), and superior to transplants from cadaveric, HLA-matched kidney donors. The long-term results of these living donor kidney transplants can be expressed in terms of graft half-life. That is: the number of years at which 50 percent of the grafts is still functioning.

Living donor transplants with a full HLA-match between related donor and recipient result in a half-life of 26 years; in case of a haplo-identical tissue match the half-life is around 13 years. The same goes for the half-life of grafts from an unrelated live donor. Finally, the half-life of cadaveric grafts is approximately 10 years (Har00). And even where the results of cadaveric grafting have improved considerably in recent years, the superior outcome of living donor transplants remains.

An important aspect of living donor kidney transplants is the opportunity to avoid dialysis treatment. Research has shown that transplantation prior to the start of dialysis (so-called pre-emptive transplant) has a beneficial effect on long-term graft survival. This is of special importance in paediatric transplantation, since dialysis treatment is known to cause growth retardation.

Much research effort has gone into establishing the risk of living donation. The risk of peri-operative morbidity (less than 2 percent serious complications), and even mortality (around 0.03 percent) is small, but should not be played down
when giving information to the potential donor. The risk of adverse consequences to the health of the living donor (e.g. hypertension or impaired kidney function) has also been shown to be small: living kidney donors have a normal life expectancy. Finally, one should not ignore the fact that living donor transplants are financially cost-saving by reducing (or even avoiding) expensive chronic dialysis treatment. All in all the benefits of living donor kidney transplants more than outweigh the possible disadvantages to the donor.

An important recent development is the laparoscopic method for donor nephrectomy. Instead of removal through classical ‘open’ surgery, in this procedure the kidney is removed via a minimally invasive procedure using an endoscope. The advantages to the donor are claimed to be: a smaller scar and less pain, a shorter period of hospitalisation, and rapid rehabilitation. This new technique requires further standardization and assessment.

These past years a debate has started concerning the limits of living kidney donation. In addition to family donation, involving genetically related donors, donation by emotionally related donors (in particular spouse/partner) has now been widely accepted. This is much less the case for donation by persons who are more distantly related to the recipient (e.g. friends or in-laws), or donation by persons who share no relationship at all with the recipient (the unrelated anonymous donors). Also, different types of cross-exchange between donor and recipient pairs, who are unable to donate directly because of ABO-incompatibility or the presence of reactive antibodies against the donor, now offer realistic possibilities (so-called paired kidney exchange or crossover donation).

It is important also to find adequate medical and moral justification for these new types of living donation. The Health Council concludes that genetically unrelated living kidney donors (emotionally related as well as unrelated anonymous donors) do not run greater risk to their health than genetically related living donors. In addition, the Council has established that the relevant Dutch legislation (the Organ Donation Act of 1996) does not present any obstacle to this type of donation. Again, from an ethical perspective, there are no conclusive arguments to exclude these novel types of unrelated living donation beforehand. However, in these cases it seems justified to do a careful assessment of the motives and background of the potential donor. Paid or commercial donation is rejected by the Health Council (as far as the situation in the Netherlands is concerned).

The Council thinks it is feasible in the coming years to increase the number of living donor kidney transplants in the Netherlands up to 250 per year. An
important precondition is that the actual bottlenecks in the capacity of the centres are removed.

**Transplantation of extra-renal organs from living donors**

The persistent shortage of cadaveric donor organs is the reason that today the possibilities of living donation of extra-renal organs are explored in practice. Donation of part of the liver from parent to child has been performed since 1990 and gives excellent results. The risk to the donor’s health, although not negligible, can be justified in the light of the beneficial outcome of these – lifesaving – procedures in often very young children.

A even more complex issue is the donation and grafting of part of the liver from an adult donor to an adult recipient. Because adequate liver function in the recipient requires the removal of a substantial portion (at least 50 to 60 percent) of the donor’s liver, the risk of severe complications and even death is considerable (0.5 to 1.5 percent mortality, 15 to 20 percent complications). This risk should be balanced against the prospects of the recipient: a favourable outcome of the transplant and the possibility of dying on the waiting list. One should also take into account that over ten percent of the transplanted patients face a possible re-transplant in the short run, which puts pressure on the whole liver transplant programme. For the moment, the Health Council considers living donor liver transplantation justified only in a highly select group of adult liver patients.

A special type of liver donation from a living donor is the ‘domino transplant’. This concerns patients with hereditary metabolic disease (such as familial amyloidotic polyneuropathy - FAP) for whom a liver transplant is indicated and planned. After removal the native liver of the patient is in turn transplanted to a second, often older, patient in urgent need of a donor liver. As symptoms of the disease become manifest only after a long period of time, and since they will not primarily affect the liver function, no substantial problems have been reported so far in recipients of a domino-liver.

Living donation of lung lobes, and of intestinal segments is still in an early phase of development. However, the prospects of satisfactory long-term graft function seem favourable. Transplantation of a pancreatic segment from a living donor is also performed in some centres. The risk to the donor in this operation is however considerable, whereas the outcome of these transplants is not superior to that of an organ from a cadaveric donor.
Non-heart-beating kidney donation

In the non-heart-beating donor death is determined according to cardiopulmonary criteria: irreversible apnoea and circulatory arrest following cardiac arrest. In the early days of kidney transplantation these NHB-donors have already been used, since there were at that time no scientific grounds for a precise determination of death on neurological criteria (brain death). After the (almost) universal acceptance of brain death criteria in 1968 (Harvard criteria) the use of NHB donors was discontinued in the seventies. However, the acute shortage of cadaveric donors has rekindled the interest in this type of donation. In the Netherlands use has been made of NHB-donors since 1980 (in the Maastricht centre). As of 2000 all transplant centres in the Netherlands perform NHBD procedures and at present around 30 percent of all transplantable donor kidneys come from NHB donors.

Although determination of death on cardiopulmonary criteria is considered to be the ‘classical’ method, the Health Council has observed that nevertheless some substantial differences in opinion exist concerning the steps to be followed and the due caution that should be exercised. In fact, proper robust scientific foundation of the criteria for irreversible circulatory arrest is lacking, and at present no specific procedures are outlined in the Organ Donation Act (in contrast to the procedure required for brain dead patients, as outlined in the Brain Death Protocol).

The Health Council holds the view that the death of a potential donor can be assumed with certainty, if a situation of irreversible circulatory arrest has been existing during at least five minutes. After this period all cerebral functions are irretrievably lost as well. After observing this five minute no-touch interval, one may start preservation of the organs, in particular cooling of the kidneys inside the body (in situ preservation) using hypothermic perfusion. To preserve organs from NHB-donors several methods have been developed: preservation on ice (simple cold storage), the already mentioned in situ preservation, and preservation of kidneys outside the body with the help of machine perfusion. To assess the viability of these organs before they are implanted, several techniques have recently been developed. However, a truly reliable and validated test is still not available.

The most important issue, however, is the outcome of non-heart-beating donor transplants. Although NHBD kidneys usually show delayed graft function after implantation, when compared to kidneys from heart-beating donors, there is in the long run no real difference in graft survival and graft function between
these kidneys. The Health Council therefore concludes that NHBD kidneys should no longer be considered ‘marginal’ or second best.

The NHBD procedure has some aspects that carry special ethical and legal importance. Besides the procedure for the determination of death, this concerns the timely start of organ preserving measures and getting consent for the removal of organs. When a patient dies in hospital after a decision has been taken to withhold or withdraw further life-prolonging treatment (ventilator switch-off procedure), it is usually known beforehand whether the donor of the relatives consent to donation, and proper arrangements can be made for the final goodbye to the deceased.

However, if the situation concerns a patient who dies in the Emergency Care department after an unsuccessful resuscitation effort, or a patient who is found to be dead on arrival, the NHBD-procedure has to be carried out under great time pressure. Problems arise when consultation of the national Donor Register shows that the deceased has left the decision to donate to his relatives or has not taken the step to register his will at all. Often in these cases, the relatives are not present in the hospital to give their consent, and preservation of the organs can no longer be postponed, because of the risk of decay and loss after they have suffered a prolonged period after warm ischaemia. The Dutch legislator has provided for this situation by stating in the Organ Donation Act that physicians are allowed to take the necessary organ preserving measures, while they are awaiting consent for organ retrieval. In this way the option of donation is kept open to the relatives.

NHBD-donation is now practised in all university centres, and is increasingly being introduced in general hospitals. The Health Council is convinced that further development of non-heart-beating donation in these hospitals will contribute significantly to the increase of the number of transplantable donor kidneys.

**NHBD-donation of extra renal organs**

Internationally there is only limited experience with NHBD-donation of extra renal organs. Most expertise has been gained with NHBD-donation and implantation of the liver. It has been shown that livers from patients who die in hospital after a planned decision has been taken to withdraw life-support (ventilator switch-off procedure in category III NHBD donors), are viable for transplantation. The outcome of these transplants does not differ significantly from liver transplantation using an organ from a heart-beating donor (at least not in the
short run). In 2001, NHBD liver donation has started in some centres in the Netherlands.

NHB-donation of lungs is at present still in an experimental phase. The short term results look promising, but there is still uncertainty over the outcome in the long run. NHB-donation of the pancreas is presently being performed – in small numbers – in some American and Japanese centres. This procedure usually involves transplanting the pancreas simultaneously with the kidney. Immediately after implantation the kidney function is somewhat compromised when compared to transplantation with a heart-beating donor kidney. In the long run however, both the kidney and the pancreas function satisfactorily.

Recommendations

Based on a thorough analysis of the scientific state-of-the-art in living donor transplantation and non-heart-beating donation, the Dutch Health Council puts forward the following recommendations.

Organ donation in general
1 The number of cadaveric donations in the Netherlands has reached a plateau, and structurally falls short of the ever-increasing number of patients on the transplant waiting list. In the past five years this decline has been partly compensated for by an increase in both living donations as well as non-heart-beating donations. The Health Council recommends that a three-track policy be followed: cadaveric donation (from heart-beating donors) should be promoted by a broad approach (legislation, additional funds, education); at the same time specific measures should be taken to promote further increase of both living donation and non-heart-beating donation.

Living donor kidney transplantation
2 Living donor kidney transplantation generally offers patients the optimal prospects of long-term rehabilitation and improvement of their quality of life. Living donation is also justified by the limited risk to the health of the donor.
3 The option of living donation should be brought more actively to the attention of kidney patients and their relatives (but without creating a sense of obligation).
4 In the Netherlands there is scope for increasing the annual living donor transplant activity; on the basis of the present waiting list a target of 250 transplants per year seems feasible.
Living kidney donation from genetically unrelated, but emotionally involved persons (spouses, partners, in-laws, close friends) can be justified on both medical and ethical grounds.

In certain cases, living donation by an individual who is neither genetically nor emotionally related to the recipient (so-called altruistic stranger or Good Samaritan donor) can be considered. This situation requires strict preservation of the anonymity of both donor and recipient. The donor kidney should be allocated following the usual rules of allocation.

Cross-exchange donation between pairs of spouses/partners with ABO blood group incompatibility or existing reactive antibodies (positive cross-match) is acceptable on both medical and ethical grounds and should be facilitated by national or international organ exchange institutions.

There is no place for paid or commercial organ donation in the Netherlands.

The option of pre-emptive kidney transplantation deserves more attention, especially in children.

Laparoscopic nephrectomy is likely to have important advantages to the donor, but better standardization of this method and careful assessment of the outcome should be undertaken.

Follow-up data on living donors should be entered in a national registry.

Living donor liver transplantation

Living donation of liver segments by an adult to benefit a child recipient is justified, according to the Health Council, on both medical and ethical grounds.

Living donation of liver segments to benefit an adult recipient involves substantial risk to the donor, but this procedure can be justified for a select group of patients under exceptional circumstances.

The Health Council recommends that alternative options for liver donation (such as non-heart-beating liver donation) should also be assessed.

Domino transplantation of the liver offers to patients a worthwhile chance of rehabilitation.

Living donation of other extra-renal organs

Living donation of lung lobes and of intestinal segments is at present still in a developmental phase. Living donation of a pancreatic segment does not offer superior outcome over cadaveric donation.
Non-heart-beating donation
17 Non-heart-beating donation of kidneys and other organs offers an important additional source of transplantable donor organs, and should be actively promoted.
18 The expansion of NHB-donation to both university centres and peripheral hospitals should be facilitated through reaching a national consensus over relevant guidelines.
19 The procedure for determination of death on cardiopulmonary criteria for use in NHB-donation should be outlined in an updated protocol.
20 When determining the death of a potential NHB-donor, an interval of at least five minutes of circulatory arrest should be observed, during which no handling of the body or interventions should take place. Following this five-minute no-touch period organ preserving measures can be started.
21 The option of NHB-donation deserves better attention in the information offered to both the patient and the general public.

NHBD kidney transplantation
22 The results of kidney transplantation from non-heart-beating donors (in terms of graft survival and kidney function) are comparable in the long run to those of kidneys from heart-beating donors. NHBD-kidneys, in the view of the Health Council, should no longer be considered as marginal or second-best organs.

NHBD transplantation of extra renal organs
23 NHB liver donation offers a potentially important source of transplantable donor organs and should now be actively promoted, among others by developing a uniform protocol.
24 NHB-donation of the lungs and the pancreas is for the moment still an experimental procedure.
Public awareness about genetics

Public awareness about genetics deserves our attention on account of the wide-ranging applications of this branch of science within our society and the speed at which it is developing. Such developments as the discovery of disease genes, the cloning of animals, DNA research by officers of the law and genetically modified (GM) food are increasingly confronting citizens with decisions and choices that require some degree of information. It is expected that the number of applications of genetic technologies will experience a further substantial increase as a result of the unravelling of the human genome. In the past, government White Papers and Health Council advisory reports have advocated public information campaigns aimed at enabling citizens to make informed choices.

The main focus of this ‘alerting’ advisory report is on the nature of the information that is required. This leads on to a discussion of what we know about the current level of public awareness and what initiatives are of relevance in this context. The report is based on a discussion of these issues that took place at a symposium organised by the Health Council in November 2001.

This advisory report does not discuss which psychological and sociological factors influence public opinion with regard to genetics. Nor does it consider which forms of (mass) information are most effective. These issues warrant closer attention.

The question of what level of public awareness about genetics is desirable receives a two-part answer. As far as the content of this knowledge is concerned, we are talking about an understanding of the large number of differences in genes
and of the interaction between genes and the environment. The many genetic
differences that exist between individual human beings also apply in the case of
the ‘disease genes’. All human beings have genes that can trigger disease
processes in themselves and in their offspring. Increasingly often, it is possible to
provide specific counselling on those processes. It is also important for the public
to know that the effect of genes is almost always influenced by other factors,
which are referred to collectively as “the environment”. These factors include
diet and lifestyle. Awareness of these issues underlines the individual
responsibility of the citizen. Besides possessing certain specific knowledge, it is
desirable that people should know how to go about asking for genetic
counselling.

The question of what knowledge the public actually has of genetics is not an
easy one to answer. Research in this area is not only scarce, but it is also open to
criticism with regard to the methodology employed. Experience gained in the
field of clinical genetics teaches us that the heritability of disease is a
misunderstood concept. Thus it appears that some people do not seek counselling
in spite of the fact that there is a history of a particular disease in their family.

As far as the initiatives that are needed in order to raise public awareness are
concerned, the focus is placed on education, general information and the position
of the general practitioner. An obvious dichotomy arises in the sphere of
education. Only a proportion of pupils – i.e. those who opt to take a course in
biology – are informed about genetics. However, adequate public awareness
demands that the others must also gain an insight into this issue – something
which could probably be accomplished through the use of simple examples. This
requires consultation between educational experts, geneticists and officials from
the relevant ministries.

Furthermore, the public at large needs to have access to general information.
As far as hereditary diseases are concerned, it is possible to consult a general
practitioner. Discussion between clinical geneticists and GPs could improve this
process. Information can also be provided via the internet, which entails making
the public aware of informative websites. One such site is the Erfocentrum, a
 genetic resource and information centre to be found at www.erfelijkheid.nl. The
dissemination of information to ethnic minorities is an issue that warrants special
attention. Research has shown that child mortality within this population group is
substantially higher than the national average in the Netherlands, with hereditary
diseases being an important contributory factor.
Conclusions

• The rapid advancement of scientific knowledge in the field of genetics is constantly giving rise to new applications for these technologies (in areas such as health care and food production). Citizens are required to make an ever-increasing number of choices in this area. Nevertheless, little is known about the level of awareness, and about possible misconceptions, in relation to genetics within the public at large.

• A substantial proportion of the students in secondary education receive no instruction on genetics.

• Owing to a lack of knowledge and misconceptions, people sometimes fail to seek counselling about genetic problems in situations where such advice is, in fact, required.

Recommendations

• Further research needs to be conducted into public awareness and attitudes in relation to genetics.

• All students should, as part of their education, be familiarised with the fundamental principles of genetics. Consideration should be given to the possibility of starting this process in primary schools.

• Key elements of genetics that merit thorough consideration are the enormous range of genetic variation and the interaction between genes and environmental factors such as diet and behaviour.

• General information and adequate referral to clinical genetics centres are important components of genetic counselling. This ideally requires an information service of the type provided by the Erfocentrum, and raising of GP awareness with regard to referral.
Therapeutic exercise

Therapeutic exercise is the prescription of muscular contraction and bodily movement ultimately to improve the overall function of the individual and to help meet the demands of daily living. It involves the positive and progressive application and adjustment of stress and forces of the appropriate type and amount to the body system to correct an impairment, improve musculoskeletal function, maintain a state of well being, or prevent dysfunction without causing injury.

Exercise therapy in the Netherlands

In the Netherlands, exercise therapy is practised by physiotherapists, Mensendieck exercise therapists and Cesar exercise therapists. In 2002, 17.2 percent of the Dutch population were seen by a physiotherapist. In 1985, this percentage was much lower, not even 10 percent. About 90 percent of the patients seen by a physiotherapist, Mensendieck exercise therapist or Cesar exercise therapist in the primary health care system are referred by their general practitioner. Sixty percent of these patients are between 25 and 55 years of age. Patients aged 55 and above are more often referred to a physiotherapist than to a Mensendieck exercise therapist or Cesar exercise therapist.

Most patients (87.5 percent) referred to a physiotherapist have disorders of the musculoskeletal system. A small proportion of referred patients have disorders of the sensory and nervous system or disorders of the respiratory
system, 7.8 and 1.7 percent respectively. Most of the patients referred to a physiotherapist or exercise therapist have neck or back complaints. Almost 75 percent of the patients referred to a Mensendieck exercise therapist or Cesar exercise therapist have complaints for more than 3 months. In contrast to this percentage, only 38 percent of the patients referred to physiotherapists have chronic complaints (> 3 months). Only a small portion of the patients who are referred to a physiotherapist (10.7 percent), Mensendieck exercise therapist (4.4 percent) or Cesar exercise therapist (5.7 percent) meet the criteria for reimbursement of the costs of long-term treatment.

The treatment given by exercise therapists consist of giving advice and therapeutic exercises. Physiotherapy treatment consist of giving advice, exercise therapy, massage therapy, or physical applications (e.g. laser-, electrotherapy or ultrasound therapy) or a combination of these applications. Most patients (83.9 percent) are individually treated in the physiotherapists practice; 11.9 percent are treated at home and 4.0 percent are treated in an institution (nursing home, residential care home). Only 2.0 percent of patients are treated in groups. Cesar and Mensendieck exercise therapists treat more than 95 percent of their patients on an individual basis, at their practice. Other patients are visited at home. In the physiotherapy practice, patients receive on average 10.9 treatments. There is considerable variation in the number of treatments given. On average, Mensendieck and Cesar exercise therapists give each patient 9.4 and 11.2 treatments respectively. Here, too, there is large variation in the number of treatments given.

The costs of exercise therapy in the Netherlands

In 1999, the Netherlands spent 36 billion euros on the health service. The combined costs of physiotherapy, Mensendieck exercise therapy and Cesar exercise therapy, are 2 percent of the total Dutch health care expenditure or 725.7 million euros. Almost half of the costs are related to musculoskeletal disorders. Neck and back problems are responsible for a quarter of the total costs of exercise therapy and physiotherapy.

Effectiveness of exercise therapy

The committee, responsible for this advisory report, has investigated the effectiveness of exercise therapy for disorders of the musculoskeletal system and connective tissue, the nervous system and sense organs, the respiratory system
Therapeutic exercise and the cardiovascular system. It selected disorders which are commonly treated by exercise therapists and physiotherapists, and which are associated with a considerable burden of disease. On the basis of a comprehensive analysis of the scientific literature (a review of systematic reviews), the Committee has drawn the following conclusions:

- Exercise therapy has been shown to be effective for patients with: cystic fibrosis, chronic obstructive pulmonary diseases (COPD), claudicatio intermittens, osteo-arthritis of the knee, as well as subacute and chronic low back pain.
- There are indications that exercise therapy is effective in patients with Parkinson's disease, ankylosing spondylitis, osteo-arthritis of the hip, and in those who have suffered a stroke.
- Exercise therapy is not effective in patients with acute low back pain.
- None of the studies showed that exercise therapy was harmful.
- There is insufficient evidence to support or refute the effectiveness of exercise therapy for patients with rheumatoid arthritis, shoulder complaints, neck complaints, RSI, asthma and bronchiectasis. For these disorders, the number of studies of good methodological quality is not sufficient to draw conclusions.

For almost all disorders, it is not yet clear which type of exercise therapy is the most effective (for example, individual treatment or group treatment). In patients with chronic low back pain, exercise therapy is more effective than continued care by their GP.

**Recommendations for the health service**

There is clear evidence that exercise therapy is effective for various disorders. Beside it, exercise therapy was not found to be harmful. Therefore, the Committee recommends that the trend in physiotherapy to emphasise exercise therapy should be strongly supported. In a number of disorders, there is insufficient evidence to support or refute the effectiveness of exercise therapy. For these disorders, the Committee recommends to investigate the effectiveness of exercise therapy. The literature survey has shown that exercise therapy is not effective in patients with acute low back pain. Therefore, the Committee recommends these patients not to be treated with exercise therapy. However, patients with acute low back pain are advised to remain active.
The above recommendations relate to the use of exercise therapy by physiotherapists, Cesar exercise therapists or Mensendieck exercise therapists. However, also GPs and medical specialists are important disciplines as they refer these patients for exercise therapy. Given the lack of relevant data, the Committee is unable to determine whether the indication for exercise therapy used by GPs and medical specialists is adequate. In the case of disorders for which exercise therapy has been proven to be effective, or where there are clear indications of its effectiveness, the Committee recommends that the use of exercise therapy should be considered, as a worthwhile option.

**Recommendations for research**

The Committee is unable to support or refute the effectiveness of exercise therapy in a number of disorders, due to a lack of systematic reviews and randomised controlled trials of good methodological quality. However, a lack of evidence or insufficient evidence is not a proof that exercise therapy is ineffective. Based on the frequently found favourable effects, the Committee recommends that the effectiveness of exercise therapy should be more intensively investigated. The Committee endorses a recent advisory report on physiotherapy, issued by the Advisory Council on Health Research, which gives priority to the evaluation of exercise therapy. With regard to future research, the Committee advises that (1) for disorders where evidence is lacking or insufficient, the effectiveness of exercise therapy should be further investigated according to current guidelines for the methodological quality and reporting of randomised controlled trials and systematic reviews; (2) the effectiveness of the various types of exercise therapy be compared; and (3) methods to maintain in the long term the short-term effects of exercise therapy should be developed and evaluated.
Inactivation of micro-organisms in blood

Work has been under way for some time in the field of blood-transfusion medicine on the development of techniques for disinfecting donated blood. If it were to be 100% successful, this approach would offer the major advantage of removing all pathogenic micro-organisms from donor blood, even those for which the blood currently is not – or cannot be – tested. Theoretically, the introduction of these so-called pathogen inactivation techniques would mean that the selection of donors and the testing of the blood for the presence of micro-organisms would become matters of secondary importance.

Various research groups and pharmaceutical companies are working on inactivation techniques based on compounds that penetrate genetic material (DNA or RNA) of micro-organisms and then bind inextricably with it. As a result, the micro-organisms are no longer able to proliferate and perish. Because the compounds used can also bind to human genetic material, laboratory research into the safety of the technique is particularly important.

The inactivation techniques for platelets, transfusion of which accounts for around 20% of all transfusion procedures, are now so advanced that routine use is considered to be a possibility. Here the Health Council’s Blood Working Group acts as committee and gives its opinion on the desirability of introducing inactivation techniques in the Netherlands. It bases this opinion on an inventory of the available scientific research.
Research results

The techniques developed have undergone various forms of testing in the laboratory. Inactivation experiments have been performed with viruses and, to a lesser extent, with bacteria and parasites. Inactivation of viruses usually results in a reduction of at least ten thousand-fold. In the case of extremely large quantities of micro-organisms, however, the inactivation techniques appear to result not in total inactivation but merely a numerical reduction. This limitation of the technique places question marks over the possibility of dispensing with other safety measures when introducing inactivation techniques.

Experiments with blood products such as platelets, plasma and red blood cells demonstrate that, although the products may well still conform to the relevant quality requirements, the treatment usually has a negative impact on quality.

The toxicological research conducted to date has largely focused on the question of whether the substances used to treat the blood products, which bind to DNA or RNA, still elicit harmful effects following completion of the procedure. The results of the research indicate that this is not the case. However, it is not clear what consequences exposure in the long term, or – in the case of patients receiving blood products on a regular basis – repeated exposure to small quantities, might have. Owing to the limitations of the research conducted to date, a definitive verdict on the safety of the techniques will probably only be possible following large-scale administration, as in the case of standard use in bloodbanks or hospitals – especially if the adverse effects occur only rarely.

There have been few publications to date on clinical research involving inactivation techniques. Most of the data is derived from two phase-III studies with amotosalen, a compound based on a group of substances known as psoralens. The American SPRINT trial showed that patients who were given platelets treated with amotosalen required 35% more blood transfusions than the patients who received platelets treated in the standard manner. In the European euroSPRiT trial, with a smaller number of patients, the patients who were given platelets treated with amotosalen did not require statistically significant more transfusions than the patients given conventionally treated platelets. This research shows that there is no statistically significant difference between the “corrected count increment” (i.e. the increase in the number of platelets following correction for the patient’s body surface area) in patients given amotosalen-treated platelets one hour after transfusion and the increase recorded in patients given the conventionally treated platelets. Twenty-four hours after
transfusion, however, the corrected count increment in the patients receiving amotosalen-treated platelets was lower than that recorded in the patients given the conventionally treated platelets. In the research with compounds other than amotosalen, too, there is evidence to suggest that the treatment of platelets or red blood cells results in loss or reduced survival of the product.

Opinion on introduction

The committee advises against the introduction of inactivation techniques for micro-organisms in blood products at this point in time.

The committee arrives at this decision in view of the paucity of published clinical research. There is, at present, only one publication on phase-III research and there is no published clinical research with the transmission of micro-organisms via blood transfusion as its endpoint. Research with such an endpoint would, in fact, require vast numbers of patients in view of the fact that transmission already occurs very rarely even with the existing safety measures.

In the Netherlands the administration of blood products has, over time, become a progressively safer medical procedure as far as the transmission of micro-organisms is concerned. The residual risks of blood transfusions for which inactivation techniques would be beneficial are: virus infections in the period between the penetration of the virus and the moment at which its presence becomes detectable by means of tests (the so-called “window” phase); infections with micro-organisms for which testing is not yet performed; bacterial infections caused by contaminated platelets; and parasitic infections. A number of these risks have already been reduced through the adoption of measures such as the testing of platelets for bacterial contamination by means of culturing.

Inactivation has no effect on the other residual risks, such as the mixing-up of blood products and transfusion-related acute lung injury. These risks will assume still greater prominence if the provisional data on the reduced effectiveness of the treated blood products is confirmed. This could, after all, mean that patients will be administered blood products more frequently than at present.

The committee anticipates that research designed to determine the complete chain of events that occurs during blood transfusion – such as, for example, the recently commenced programme of the Association for Transfusion Reactions in Patients (TRIP) – will provide quantitative data concerning the residual risks of blood transfusion in the Netherlands. This data may pave the way for a modification of the position adopted here with regard to the status of inactivation techniques.
At present, pneumococcal vaccination is not carried out on any great scale in the Netherlands. Among adults, the vaccine is administered only to individuals who are at substantially increased risk of pneumococcal infection. These include asplenia patients, people with low immunity and those suffering from Hodgkin’s disease. At the request of the Minister of Health, Welfare and Sport, a Health Council committee has examined the scientific desirability of making vaccination available to additional groups of adults. In particular, the Minister wished to know whether the Council would advise combining pneumococcal vaccination with the annual influenza vaccination made available to over-sixty-fives.

On the basis of an assessment of the scientific evidence undertaken for the Health Council by the Dutch Cochrane Centre, the Committee has concluded that extension of the indication for pneumococcal vaccination is not scientifically justified under the present circumstances. Little can yet be added to the information presented in the Council’s 1982 report on this subject.

The scientific evidence currently available does not suggest that combined influenza and pneumococcal vaccination is advisable for over-sixty-fives. Nevertheless, the Committee wishes to see comparative research conducted to shed more light on this matter.
With regard to pneumococcal vaccination for people with particular conditions, the Committee’s recommendations are on three levels:

- Vaccination is definitely recommended only for people in groups with a very high mortality risk. These include people suffering from asplenia, sickle-cell anaemia or liquor leakage. Everyone in these groups should be inoculated against pneumococci and should always have antibiotics at their disposal.

- Vaccination should be considered, taking account of the circumstances of the individual case, for people suffering from Hodgkin’s disease, non-Hodgkin’s lymphoma, HIV, myeloma, chronic lymphatic leukaemia, an autoimmune condition, renal disease or alcoholism, cirrosis, as well as for people receiving immunosuppressives or who have undergone bone marrow or organ transplantation.

- Vaccination is not recommended for people diagnosed with hypogammaglobulinemia or agammaglobulinemia, solid tumours, diabetes, chronic respiratory disease or chronic heart failure. The Committee does nevertheless recommend careful research into the last three risk groups, with particular attention focused on the vaccine type.
Tetanus prophylaxis in injuries


Anyone with an open wound that has been in contact with soil is at risk of infection by the bacterium that causes tetanus. An infection of this kind can have serious after-effects if the individual has never been immunised against tetanus or if it has been too long since their last immunisation. However, these after-effects can be countered using tetanus immunoglobulin, an antibody preparation made from human blood. This advisory report addresses the issue of whether tetanus immunoglobulin should be routinely administered in the course of wound treatment, and whether immunisation (or re-immunisation) is required. The advisory report will be presented to the Minister of Health, Welfare and Sport.

The request for this advisory report was prompted by the suspicion that tetanus immunoglobulin is sometimes administered unnecessarily. Furthermore, a variety of different protocols are in use throughout the Netherlands. The report of an investigation into this issue (which was carried out at the request of the Inspectorate for Health Care) was therefore sufficient cause for the Health Council to produce an advisory report on the use of tetanus immunoglobulin.

On the basis of an efficacy analysis, it is recommended that the following groups receive tetanus prophylaxis if a wound is sustained:
1. individuals who are known not to have been vaccinated (dose of tetanus immunoglobulin and vaccination at 0, 1 and 6 months);
2. individuals who are known not to have completed a full course of vaccination (administer dose of tetanus immunoglobulin and supplement with missing vaccinations);
3 individuals above the age of 20 who are assumed to have been vaccinated (dose of tetanus vaccine), plus a dose of tetanus immunoglobulin for men born prior to 1936 and women born prior to 1950;
4 fully vaccinated individuals who received their last dose of vaccine more than ten years previously (dose of tetanus vaccine);
5 those infected with HIV with an impaired reaction on vaccination and other individuals with compromised immunity (dose of tetanus immunoglobulin and vaccination at 0, 1 and 6 months).

If they should sustain a wound, individuals who have been vaccinated in accordance with the National Vaccination Programme and who were last vaccinated no more than ten years previously need neither tetanus immunoglobulin nor a supplementary dose of vaccine.

This approach provides adequate protection for groups that are vulnerable to infection. It also avoids large numbers of unnecessary injections which would otherwise involve considerable expense, as well as unpleasant symptoms (pain and stiffness) for those involved.
Legionnaire's Disease

In 1976, the Legionella bacterium was identified as the pathogen which causes Legionnaire’s Disease. This followed an incident in which American war veterans became ill following their stay at a hotel in Philadelphia. Being difficult to culture, the bacteria had not previously been identified as a pathogen. It had apparently proliferated in the hotel’s air-conditioning system. This bacteria’s unusual characteristics meant that it was able to proliferate at temperatures of between 20°C and 45°C in the biofilm lining mains water systems and other fittings. Individuals can then become infected by breathing in an aerosol of contaminated water. Soon thereafter, Legionnaire’s Disease was also found in the Netherlands. It emerged that the Legionella bacteria was present in the mains systems.
water systems of several hospitals. Accordingly, the first Health Council advisory report focused heavily on this nosocomial problem.

Legionnaire’s Disease or Legionellosis has various forms. Individuals can come into contact with Legionella without becoming ill, as shown by the presence of antibodies in their blood. Alternatively, the disease can manifest itself as a mild dose of flu. Finally, victims may go on to develop pneumonia. The fact that Legionella pneumonia can be very serious, even lethal, was illustrated once again by the events in Bovenkarspel.

**Legionella causes eight hundred cases of severe pneumonia every year**

It is difficult to establish the true scale of the Legionella problem. In this advisory report, the Committee has restricted itself to the number of patients admitted to hospital with Legionella pneumonia. Even making an estimate of that figure proved to be no easy matter. The disease is difficult to diagnose, the mandatory notification procedure leaves much to be desired and is also very erratic, depending on the course of current events.

In 1998, there were 0.26 notifications per 100,000 head of population. In 1999, following Bovenkarspel, this figure had risen to 1.7 per 100,000 head of population, which corresponded to 279 patients. Using another approach, the Committee arrives at an annual figure of 800 cases of Legionella-caused pneumonia that are treated in hospital. There are about 110,000 cases of pneumonia in the Netherlands each year. Of these, about 15 percent are admitted to hospital (16,000) and about 5 percent of these (800) are caused by Legionella. Legionella pneumonia has a mortality of about 10 percent (80 individuals per annum). None of these figures takes account of the continually changing circumstances and the gradual implementation of numerous rules and recommendations.

One interpretation of this data is that we do not yet fully understand the scale of the problem. Another interpretation is that this problem fades into insignificance when set against the large number of pneumonia cases in general. Finally, a third interpretation is that when dozens of individuals die because technical deficiencies cause our water supply to become contaminated with lethal bacteria, this is a ‘grave situation’ and a ‘major problem’.

When we compare the above-mentioned figures to the current standards for drinking water, there is certainly an unreasonably large risk of catching Legionella. The risk of acquiring an infection from drinking water should be less than 1:10,000 individuals per annum. The maximum permissible mortality risk level is defined as 1:1,000,000 individuals per annum while a negligible
mortality risk level is equivalent to 1:100,000,000 individuals per annum. Compared to these converted standards, the Committee's estimated mortality risk level for Legionella pneumonia is between five and five hundred times as high.

**Policy recommendations**

There are four areas in which the risk of Legionella infection can be reduced at acceptable cost, without involving a major impact on the environment. The Committee that drew up this advisory report took the view that policy should, at the same time, address the following points.

**European agreements**

About half of these Legionella patients become infected while abroad, mostly in South European holiday resorts. The greatest gains can therefore be made by working within a European framework to implement modern guidelines in all member states.

**Rapid diagnosis and treatment**

It is impossible to completely eliminate Legionella from mains water systems and fittings. Accordingly, the focus should be on diagnosis and treatment. Serious illness and mortality can be avoided by rapidly reaching a diagnosis and through the use of prompt and adequate therapy in cases of suspected Legionella pneumonia. To this end, the Committee has included a number of specific recommendations in this advisory report.

**Modification of water fittings**

In the Netherlands the problem can be tackled at source. Mains water systems and water atomising equipment should be subjected to a risk analysis. If indicated, a management plan should be drawn up with the aim of modifying the system to reduce the risk.

The Committee cannot endorse the addition of monochloramine or other chemical disinfectants to the entire Dutch mains water distribution system. The adverse effects on the environment, on the quality of our excellent water, and on the service life of pipelines and fittings, as well as the expense involved, massively outweigh any possible gains.
Extensive legislation has been drafted over the years and this is now in place. Nevertheless, some points still require attention to ensure that high-risk systems are not overlooked. This applies to large-scale events where water atomisers are being used, residential properties and small companies, water atomisers that are not connected to the mains water system, drilling rigs and ships. The Committee also feels that legislation is no substitute for responsible attitudes on the part of those who wield authority over the systems in question.

Research

Further rationalisation of policy with regard to Legionella is dependent on greater understanding and on technical improvements. Accordingly, every case of Legionella pneumonia should trigger a systematic search for the source of infection. Methods used in molecular biology, such as the polymerase chain reaction (PCR), should be introduced for the detection of Legionella bacteria in mains water and for the purpose of diagnosing patients. There should also be more research into the connection between Legionella growth in tapping points and the risk of disease. Furthermore, materials must be developed for pipelines, couplings and taps which make it more difficult for these structures to be colonised by Legionella. Finally, scientific research should be initiated into the effectiveness of alternative control methods in mains water systems and fittings.

Political weighing of costs and benefits

Measures aimed at keeping mains water systems and water atomising equipment ‘healthy’ are set out in the *Tijdelijke Regeling legionellapreventie in drinkwater* (Provisional Scheme for the prevention of Legionella in drinking water) and in the *Ontwerpbesluit tot wijziging van het waterleidingbesluit* (Draft decree for the amendment of the Water Supply Decree). The political debate regarding these documents focuses on the affordability of the measures being put forward. An attempt should therefore be made to find a rational risk stratification, which will provide the basis for a sensible approach to priority setting. The elements to be considered here are those costs and benefits that can be expressed in quantitative terms, the vulnerability and susceptibility of exposed individuals, as well as the social acceptability (or unacceptability) of certain risks. Overdue maintenance should be performed, irrespective of the efforts allocated to the prevention of Legionella pneumonia.
The Committee notes that the issue of affordability is another fundamental area of tension. In medical terms, the costs and benefits of various activities are usually compared on the basis of the costs per quality adjusted life year (QALY). In this way, measures to protect the environment can be compared with medical interventions. On the other hand, environmental issues involve more than QALYs alone. We feel responsible for the environment, which is temporarily entrusted to our stewardship, and we want to bequeath it to future generations in pristine condition. Considerably larger sums of money are spent in this context than is usual by medical standards. Policy-makers should therefore ask themselves whether they see the Legionella problem from the viewpoint of the health service or that of environmental policy. On that basis it can be decided if and how much extra effort is warranted.
Vaccination of children against hepatitis B


Request for advice

On 1 March 2003, the National Vaccination Programme (NVP) was extended to include vaccination for the children of families in which one or both parents come from a country where hepatitis B is common. Such children are at increased risk of coming into contact with carriers, whether within the family, within their social circle in the Netherlands or when visiting their parent’s (or parents’) country of origin. This vaccination was prompted by an advisory report which the Health Council produced in 2001. These children are vaccinated with half a dose of vaccine (‘child dose’) on three separate occasions, at the ages of two months, four months and eleven months.

Another group consists of children whose mothers are carriers of the hepatitis B virus (hereafter referred to as ‘children of HBsAg-positive mothers’). Members of this group have been routinely vaccinated since 1989. The vaccination schedule used in the case of these children (who become contaminated with the virus at birth) differs from that used for the new group. Hepatitis B antibodies are administered immediately after birth, followed by vaccination with a whole dose of vaccine (‘adult dose’) on four separate occasions, at the ages of two months, three months, four months and eleven months. The antibodies provide immediate protection but this is passive in nature. It is intended as a stop-gap measure, until active protection has been built up through vaccination. The vaccination schedule was originally supported by
targeted research. Although it was formally included in the NVP only recently, vaccination for this group has used the latter’s organisational structure and vaccination sessions from the very beginning.

The State Secretary for Health, Welfare and Sport has decided that, with effect from 1 March 2003, the vaccination schedule for the group of children of HBsAg-positive mothers will be adapted to conform with the new group. This means that there will be three separate vaccinations (at the ages of two months, four months and eleven months) instead of four and the child dose will be used rather than the adult dose. The administration of hepatitis B antibodies immediately following birth is to be continued. The State Secretary has asked the Health Council whether it is possible to provide scientific support for the amendment to the vaccination schedule that affects children whose mothers are carriers. In addition to assessing the efficacy of the vaccination schedule, the Committee evaluated the workings of the programme’s broader aspects.

Risks

Mothers who are carriers of the virus will contaminate their children when giving birth to them. Not all children who are contaminated with the virus at birth go on to develop an actual infection. In the case of mothers who have tested positive for the surface antigen (HBsAg positive) but not for the e antigen (HBeAg negative), the risk of infection is about 15 percent. However, for the new-born children of mothers who are both HBsAg positive and HBeAg positive (an indication that they are more infectious) this risk is about 90 percent. Infection can also be transferred after birth, via breast-milk for example, or via cuts in the nipples or skin. The risk that newly infected individuals will become carriers is highly dependent on their age. Young children have a very high risk of becoming carriers. In the case of new-born children, the risk that an infection will become chronic and that they will go on to become carriers is about 90 percent.

If the children of carriers are not treated, many of them will also go on to become carriers. The dangers posed by this situation include further spread of the disease, chronic liver inflammation, liver cirrhosis and primary liver cancer. Transmission from mother to child is one of the mechanisms that maintains the spread of hepatitis B in a population. Given the chronic complications involved, this is enormously costly for the infected individuals and for society in general.
**Vaccination**

In the vast majority of cases, vaccination soon after birth can prevent new-born children from becoming carriers. Accordingly, in addition to the vaccination of infants or pre-adolescents, the World Health Organization (WHO) attaches great importance to screening pregnant women and to vaccinating the children of carriers. A programme to tackle this particular issue was introduced in the Netherlands in November 1989.

On an annual basis, that screening and vaccination programme prevents about 200 infections and the creation of 180 new carriers. Each year, at least 1000 children are born to HBsAg-positive mothers. About 200 of these mothers are also positive for the e antigen. In the absence of a vaccination programme, this would lead to about 300 infections and about 270 new carriers as a result of transmission during birth.

The Committee considers vaccination of the children of HBsAg-positive mothers to be both a form of prevention and a medical treatment (post-exposure prophylaxis). This is, after all, not simply about the prevention of hepatitis B at the population level, it is also a matter of providing health care for the individual. The situation is fundamentally different from that of the children of families in which one or both parents were born in a country where hepatitis B is endemic, but where the mother is not HBsAg positive.

**Effectiveness of the vaccination**

The indication of a vaccination for a specific group should be based upon targeted research into its efficacy (here: the percentage of children shown to have been prevented from becoming carriers) of a specific vaccine administered in accordance with a defined vaccination schedule. After taking stock of scientific insights into the effectiveness of vaccinating the children of HBsAg-positive mothers, the Committee has concluded that there is no scientific basis for the vaccination schedule that was introduced on 1 March 2003. The Committee has identified various vaccination schedules that are worthy of recommendation.

Regarding the use of half doses of vaccine (‘child dose’) and a vaccination schedule consisting of three doses, the Committee has concluded that both have some degree of scientific support, provided that the initial dose of vaccine is given immediately after birth, together with the hepatitis B antibodies.
Effectiveness of the programme

The Committee then evaluated the workings of the programme's broader aspects. In addition to the effectiveness of the vaccination schedule, the coverage of the programme is implicated, i.e. the percentage of children of HBsAg-positive mothers who have completed the full programme.

The programme was first linked to the NVP for purely pragmatic reasons. Modifying the programme to conform to the NVP has, in the Committee’s view, led to several adverse compromises, including postponement of vaccination and relatively low coverage. The individuals and institutions associated with the programme’s implementation should be well aware of the programme’s medical nature and purpose. The Committee has the distinct impression that this is not the case.

Another important conclusion is that the national programme has by no means achieved the worthy goal of full coverage. The average coverage of approximately 90% that has been achieved by ‘hitching a ride’ with the NVP is quite inadequate.

That a higher coverage is possible, is demonstrated by the programme as implemented in Amsterdam. There they opted for a different approach right from the start, one that did not involve the NVP. The active approach adopted there is in accordance with WHO recommendations. It involves starting vaccination as soon as possible after birth, which complies more fully with the programme’s objective. It has been shown that approaches of this kind can achieve almost total coverage.

Recommendations

The Committee recommends that the feasibility of using the Amsterdam model in other parts of the country be investigated. Given the enormous cost of hepatitis B in new-born children, to the infected individuals and to society in general, and the expected gains from an active approach and strict supervision of the programme, the Committee feels that the extra effort involved would definitely be worthwhile.

In the new approach the Committee recommends that, in accordance with WHO recommendations, 150 IU of hepatitis B antibodies be administered immediately after birth, that an initial dose of vaccine (child dose) be administered as soon as possible after birth (but no later than the infant’s first
week of life), the second dose should be given at the age of one month and the third dose at six months.

The Committee takes the view that administration of the initial dose of hepatitis B vaccine by the midwife or by the physician attending the birth would certainly be in keeping with the Netherlands’ excellent tradition of perinatal care. Midwives are qualified to carry out procedures of this kind.

At the age of 12 months, serological tests should be carried out to determine whether the vaccination has resulted in the production of antibodies (anti-HBs) or whether the child has become a carrier (HBsAg). In the latter case, treatment should be intensified.

A switch to the proposed approach should be implemented with great care, and under the strict supervision of a programme committee. It would be a good idea to test this concept in a few selected regions first.

While they may vary from place to place in terms of procedural detail, active supervision and regular evaluation are essential elements of the programme. The Committee’s vision involves supervision and evaluation at local level by the Municipal or Regional Public Health Services, and at national level by the Health Care Insurance Board’s Coordinating Committee for Prenatal and Postnatal Screening.

If, contrary to the Committee’s preference, there is a desire to retain the link to the NVP, the Committee recommends that a schedule be introduced that involves vaccination immediately following birth and at the ages of two months, four months and eleven months. The dose to be used in conjunction with this schedule should be the child dose.
In 1992, the former Food and Nutrition Council of the Netherlands published dietary reference intakes. These recommendations for the intake of nutrients were primarily aimed at the prevention of clinical symptoms and biochemical signs of deficiencies. In recent years, increasing numbers of studies have shown that certain nutrients can also help to prevent chronic diseases. Partly as a result of this, the Health Council decided to review the dietary reference intakes. The Committee on Dietary Reference Intakes, which is charged with this task, sets out its findings in a series of recommendations. The first report, containing the dietary reference intakes for calcium, vitamin D, thiamine, riboflavin, niacin, pantothenic acid and biotin, was published in July 2000.* A year later, the second report was published, with the dietary reference intakes for energy, proteins, fats and digestible carbohydrates. The present report contains the dietary reference intakes for vitamin B₆, folate and vitamin B₁₂.

The term ‘dietary reference intakes’ is a collective term for the ‘estimated average requirement’, ‘recommended dietary allowance’, ‘adequate intake’ and ‘tolerable upper intake level’. The recommended dietary allowance and adequate intake are similar terms: they both reflect the intake level at which no signs of deficiency are observed and the risk of chronic diseases (if influenced by the nutrient concerned) is kept as small as possible. The Committee preferably determines the recommended dietary allowance, defined as the estimated

* The reports of the Health Council of the Netherlands are available at www.gr.nl.
average requirement plus twice the standard deviation of the requirement. It can also be calculated by multiplying the estimated average requirement by the result of one plus 0.02 times the coefficient of variation of the requirement. If the available data are not sufficient to determine the estimated average requirement, the Committee determines the adequate intake instead of the recommended dietary allowance. Given a requirement with a normal distribution, the estimated average requirement is the level of intake that is adequate for half of the population. Finally, the Committee specifies the tolerable upper intake level. This is the level of intake above which there is a chance that adverse effects will occur.

The dietary reference intakes are intended for use by the healthy section of the population. The Committee gives separate values for infants, young children, adolescents, adults and the elderly. In many cases, the Committee makes distinctions on the basis of gender. It also establishes dietary reference intakes for pregnant women and for women who are breastfeeding infants. The three tables in this summary contain all of the dietary reference intakes that have been derived in this report. In this executive summary, the major changes relative to the previous Dutch dietary reference intakes are discussed, as are the differences with dietary reference intakes in use in foreign countries.

**Vitamin B₆**

The biologically active form of vitamin B₆, pyridoxal-5-phosphate, plays a role in various processes in the body, including amino acid metabolism. Reduced intake of vitamin B₆ may increase the likelihood of coronary heart diseases, but the Committee believes that this relationship has not been convincingly scientifically proved.

The bioavailability of vitamin B₆ from food — both the naturally present vitamin B₆ and the vitamin B₆ that is added to enriched foods — is estimated to be 75% of the bioavailability of vitamin B₆ from a supplement. On the basis of this, all the amounts were converted to the amount of vitamin B₆ in the food when dietary reference intakes were determined.

Because of its role in amino acid metabolism, the vitamin B₆ requirement is also determined by protein intake. According to the Committee, this association is not linear. The Committee believes that the recommended dietary allowances that have been derived in this advisory report apply for a daily protein intake of up to 150 grams. In the case of higher consumption, 0.01-0.02 milligram’s of extra vitamin B₆ should be taken for each extra gram of protein.
According to the Committee, the concentration of pyridoxal-5-phosphate in plasma is the most suitable parameter for determining the vitamin B₆ status. When there is a lack of research results of this kind, the Committee also bases the derived estimated average requirement on research that uses other status parameters, such as the tryptophan load test and the activity coefficient of aspartate amino transferase in red blood cells.

It was possible to derive the estimated average vitamin B₆ requirement and therefore also recommended dietary allowance for four groups (the age groups from 19 up to and including the age of 50, from age 51, pregnant women and lactating women). The adequate intake has been determined for all other groups. The estimated average requirement for adults was determined on the basis of the aforementioned biochemical parameters of the vitamin B₆ status. The Committee assumed that the requirement has a coefficient of variation of 20% when calculating the recommended dietary allowance. The adequate intake of vitamin B₆ for babies up to six months old was based on the average intake of infants who are exclusively fed with human milk. The adequate intakes for children and adolescents were calculated by interpolation of the values for infants and those for adults from 19 up to and including the age of 50. The extra need for vitamin B₆ during pregnancy is based on the amount deposited in the foetus and placenta; the extra requirement of lactating women is based on the average amount secreted via breast milk by mothers who exclusively breastfeed their infant.

The new Dutch values for adult males correspond well with those in Scandinavia, in Germany, Switzerland and Austria, and in the European Union; however, these reports state lower recommended dietary allowances for women, in connection with lower protein consumption. The adjustment for women was not made in the present advisory report because of the Committee’s assumption that protein intake at levels up to 150 grams per day does not affect the vitamin B₆ requirement. Dietary reference intakes for vitamin B₆ in Great Britain are linked to protein consumption; the recommended dietary allowances correspond with the new Dutch values if daily protein intake is 100 grams. Owing to the use of a higher coefficient of variation of the requirement, the recommended dietary allowances for adults are a little higher than the values determined for the United States.
For the derivation of the tolerable upper intake level, the Committee subscribed to the conclusions of the European Union’s Scientific Committee for Food. The upper limit is considerably lower than the value determined for the United States. The tolerable upper intake level was adjusted on the basis of body weight for the younger age groups.

### Folate

The biologically active forms of folate play a major role as a co-enzyme in amino acid metabolism and in the synthesis of DNA and RNA. The folate requirement is therefore relatively high during growth and pregnancy, and deficiencies first manifest in tissues with a high division rate.

Folate that occurs naturally in foods differs chemically from the synthetic folic acid that is used in supplements and in food enrichment. The dietary reference intakes in the present advisory report are expressed as the amount of food folate. It has been assumed here that the figures for the bioavailability of food folate and the bioavailability of folic acid that is added to enriched foods are 50% and 15% lower, respectively, than the figure for the bioavailability of folic acid in supplements. One member of the Committee does not agree with this approach. He believes that the scientific knowledge for this distinction is insufficient and that the variation in bioavailability between the different types of

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Table S1: Dietary reference intakes for vitamin B₆ in food*, in milligrams per day.

<table>
<thead>
<tr>
<th>(age) group</th>
<th>estimated average requirement</th>
<th>recommended dietary allowance</th>
<th>adequate intake</th>
<th>tolerable upper intake level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>man</td>
<td>woman</td>
<td>man</td>
<td>woman</td>
</tr>
<tr>
<td>0 to 5 months</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6 to 11 months</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1 to 3 years</td>
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<td>-</td>
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<td>4 to 8 years</td>
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<td>9 to 13 years</td>
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<td>-</td>
</tr>
<tr>
<td>14 to 18 years</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>19 to 50 years</td>
<td>1.1</td>
<td>1.1</td>
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</tr>
<tr>
<td>≥ 51 years</td>
<td>1.3</td>
<td>1.1</td>
<td>1.8</td>
<td>1.5</td>
</tr>
<tr>
<td>pregnant women</td>
<td>-</td>
<td>1.35</td>
<td>-</td>
<td>1.9</td>
</tr>
<tr>
<td>lactating women</td>
<td>-</td>
<td>1.35</td>
<td>-</td>
<td>1.9</td>
</tr>
</tbody>
</table>

a both the naturally present vitamin B₆ and the vitamin B₆ that is added to enriched foods

b in the case of only breastfeeding: 0.12 mg/d
c in the case of formula feeding (in connection with the higher protein content): 0.20 mg/d

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66 Health Council of the Netherlands; Reports 2003
Dietary reference intakes for folate should be expressed as the amount of synthetic folic acid.

The Committee’s assessment of the folate status is based on the concentration of the vitamin in serum and red blood cells, as well as on the concentration of homocysteine in plasma. The Committee uses the last of the aforementioned factors as a status parameter, with 15 µmol/l as the upper limit of normal physiological distribution. A great deal of research is being conducted into the question of whether further reduction of plasma homocysteine concentration through increased folate intake provides protection against cardiovascular diseases. According to the Committee, this has currently not been sufficiently demonstrated because the required research results from interventional research are not yet available. However, this research is underway and the results are expected to be published within 2 to 3 years. If these publications become available, then the dietary reference intakes for folate must be re-evaluated. The Committee believes folate’s possible protective effect against cancer has not been convincingly demonstrated.

The estimated average folate requirement for adults was determined on the basis of the three status parameters referred to above. A relatively high coefficient of variation of 25% was used in calculating the recommended dietary allowance because genetic factors also contribute to the variation in the folate requirement.* For all remaining groups, no estimated average requirement (and, therefore, no recommended dietary allowance) could be determined. The Committee therefore established adequate intakes for these groups. The derivation methods for infants, children, adolescents and lactating women correspond with those for vitamin B6. The extra folate requirement during pregnancy was estimated to be 100 micrograms per day. The Committee maintains the advice to women who wish to become pregnant that — besides their normal intake in food — during the period from four weeks before to eight weeks after conception they should also take a supplement containing 400 micrograms of folic acid to prevent neural tube defects.

The recommended dietary allowances for adults are lower than the values determined for the United States and for Germany, Switzerland and Austria, higher than the values for Great Britain and the European Union, and correspond with those for Scandinavian countries.

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* The Committee refers here to people with the TT-genotype for 5,10-methylene tetrahydrofolate reductase, who require a higher level of folate. It is estimated that approximately 12% of Caucasians and Asians have this genotype; it apparently occurs less frequently in Afro-Americans.
The Committee subscribes to the tolerable upper intake level for adults that the Health Council determined in 2000. This value corresponds with the values for the European Union and the United States. The upper limit was adjusted for the younger age groups on the basis of body weight.

**Vitamin B₁₂**

Vitamin B₁₂ is involved in two enzyme systems in metabolism. Vitamin B₁₂ has a direct influence on the metabolism of folate via one of the two systems. Vitamin B₁₂ deficiency first manifests in tissues with a high division rate (such as red blood cells, blood platelets and epithelial cells of the gastrointestinal tract) but may also cause neurological damage.

The Committee believes there is insufficient scientific knowledge on the effect of intake on the status of vitamin B₁₂ to serve as a basis for setting the standard. The Committee therefore takes the estimated average requirement for adults to be the amount of vitamin B₁₂ that is required to compensate for daily losses of 0.2% of the minimum required bodily reserve of 500 micrograms, and assumes that the body takes up an average of 50% of the vitamin B₁₂ in food. A coefficient of variation of 20% was assumed for the calculation of the recommended dietary allowance. The estimated average requirements and

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**Table S2. Dietary reference intakes for folate in micrograms per day.**

<table>
<thead>
<tr>
<th>(age) group</th>
<th>estimated average requirement³</th>
<th>recommended dietary adequate intake³</th>
<th>adequate intake³</th>
<th>tolerable upper intake level³</th>
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<td>1 to 3 years</td>
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<td>4 to 8 years</td>
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<td>150</td>
<td>350</td>
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<td>9 to 13 years</td>
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<td>225</td>
<td>600</td>
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<td>14 to 18 years</td>
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<td>≥ 51 years</td>
<td>200</td>
<td>300</td>
<td>-</td>
<td>1,000</td>
</tr>
<tr>
<td>pregnant women</td>
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<td>400</td>
<td>1,000</td>
</tr>
<tr>
<td>lactating women</td>
<td>-</td>
<td>-</td>
<td>400</td>
<td>1,000</td>
</tr>
</tbody>
</table>

³ the estimated average requirements, recommended dietary allowances and adequate intakes concern folate that occurs naturally in food

³ the tolerable upper intake levels only relate to synthetic folic acid

³ it is advisable that – besides their normal intake in food – during the period four weeks before to eight weeks after conception women should also take a supplement containing 400 micrograms of folic acid to prevent neural tube defects.
recommended dietary allowances for pregnant and lactating women, and the adequate intakes for all other groups, were derived with methods comparable to those described for vitamin B6.

The recommended dietary allowance for adults is higher than the value in the United States because a higher coefficient of variation of the requirement was used in the present advisory report. The values in Scandinavia, Great Britain and the European Union are a little lower, and those in Germany, Switzerland and Austria are somewhat higher than the new Dutch values. These differences are attributable to differing assumptions about daily losses or the required size of the bodily reserves.

The Committee shares the opinions of expert committees in the United States and the European Union that no risks appear to be associated with taking higher doses of vitamin B12 and that the available data are not sufficient to enable a tolerable upper intake level to be derived for this vitamin.

<p>| Table S3 | Dietary reference intakes for vitamin B12 in micrograms per day. |</p>
<table>
<thead>
<tr>
<th>(age) group</th>
<th>estimated average requirement</th>
<th>recommended dietary allowance</th>
<th>adequate intake</th>
<th>tolerable upper intake level</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 5 months</td>
<td>-</td>
<td>-</td>
<td>0.4</td>
<td>-</td>
</tr>
<tr>
<td>6 to 11 months</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
<td>-</td>
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<tr>
<td>1 to 3 years</td>
<td>-</td>
<td>-</td>
<td>0.7</td>
<td>-</td>
</tr>
<tr>
<td>4 to 8 years</td>
<td>-</td>
<td>-</td>
<td>1.3</td>
<td>-</td>
</tr>
<tr>
<td>9 to 13 years</td>
<td>-</td>
<td>-</td>
<td>2.0</td>
<td>-</td>
</tr>
<tr>
<td>14 to 18 years</td>
<td>-</td>
<td>-</td>
<td>2.8</td>
<td>-</td>
</tr>
<tr>
<td>19 to 50 years</td>
<td>2.0</td>
<td>2.8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥ 51 years</td>
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<td>2.8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>pregnant women</td>
<td>2.3</td>
<td>3.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>lactating women</td>
<td>2.7</td>
<td>3.8</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Overweight and obesity


With this advisory report the Health Council answers the request of the minister of Public Health, Welfare and Sport to make an inventory of the latest insights and expected scientific breakthroughs with regard to prevention and treatment of overweight and obesity.

Epidemic

Throughout the world, the prevalence of overweight and obesity* has taken on epidemic proportions. In the Netherlands, as elsewhere, there is a steady rise (increasing prevalence) in the number of individuals suffering from overweight and obesity. While it is comparable to the situation in other European countries, this increase is less pronounced than in the United Kingdom and Germany, for example. On average, 40% of Dutch adults are overweight, while 10% of the adult population is obese. It is estimated that 1 to 1.5% of adults suffer from morbid obesity.

The extent of the overweight epidemic is also clearly reflected in the increased prevalence of overweight during childhood. On average, 13% of boys and 14% of girls in the Netherlands are overweight. It seems that the most

* According to the WHO definition, adults are defined as obese (severely overweight) if they have a BMI of 30 kg/m² or more. Those with a BMI value of between 25 and 30 kg/m² are said to be overweight. The BMI (Body Mass Index) is defined as an individual's body weight (in kg) divided by the square of their height (in metres).
marked increase in prevalence occurs in young children above the age of three. If this trend continues, it is estimated that 15 to 20% of adults in the Netherlands will be obese by 2015.

Overweight and obesity are more common in poorly educated population groups and in population groups of Turkish and Moroccan origin.

Health risks

While the health risks associated with obesity have been well documented, much less is known about those associated with moderate overweight. One of the first consequences of weight gain is insulin resistance, which disrupts the normal action of insulin. Insulin resistance plays a key role in the development of metabolic syndrome. This syndrome is characterised by a number of associated metabolic anomalies such as insulin resistance, dyslipidaemia*, hypertension, and abdominal obesity. These anomalies in turn form the basis for the development of disorders such as type 2 diabetes mellitus (age-related diabetes) and its complications.

Other health risks that are associated with overweight and obesity are: cardiovascular diseases, various types of cancer, gall-bladder diseases, arthrosis, respiratory problems, gout, infertility, menstrual disorders and foetal defects. The greater the overweight the greater the risk of such comorbidity.

Of all these health risks, the increased prevalence of glucose intolerance and type 2 diabetes mellitus, is particularly worrying. In the United States this is even occurring in children. In addition, obesity is often accompanied by psychological and social problems, as well as a reduced quality of life. The morbidity associated with obesity (and, to a lesser extent, with overweight) leads to numerous (medicinal) treatments and additional work disability, as well as increased costs for the health care.

Physical inactivity and overconsumption

Over extended periods of time, a small positive energy balance leads to major changes in body weight. This means that overweight can easily develop when the energy intake is only slightly higher than the energy consumption. National food consumption surveys reveal that there was a fall in average energy intake in the Netherlands from 1987/1988 to 1997/1998. There are clear indications of a substantial decline in the level of daily physical activity in recent years. In view

* Low HDL serum cholesterol, high serum triglycerides, high LDL serum cholesterol.
of the increased prevalence of overweight, however, the extent of this decline in physical activity must more than compensate for the fall in energy intake. It therefore seems likely that the increased prevalence of overweight and obesity is due to an increasing lack of exercise, combined with relative overconsumption.

If overweight is to be prevented, it is essential that energy intake be attuned to energy use. A high-fat diet carries a greater risk of overconsumption than is the case with a low-fat diet. The exact types of carbohydrates consumed are also important, although the way in which this affects the regulation of the energy balance is not yet fully understood. Nevertheless, there is strong evidence that the sugars contained in energy-rich drinks (especially soft drinks) can easily lead to a positive energy balance. In addition, epidemiological studies have revealed a clear connection between a low-fibre diet and the risk of overweight.

Various other dietary factors can also affect energy intake, such as the energy density of the diet, portion size and meal frequency (especially 'snacking' behaviour). A diet which provides the best chance of maintaining the energy balance is one with a low energy density, and which includes plenty of fruit, vegetables and cereal products.

In terms of preventing an increase in body weight, moderate daily exercise seems to be more important than one-off peak exertion. Activities which involve a moderate degree of exertion can be sustained for longer periods of time. As a result, these achieve a relatively high degree of fat oxidation.

The current Dutch standard for healthy levels of exercise stipulates a minimum of thirty minutes of moderate exertion, preferably every day but for no less than five days per week. However, this does not seem to be sufficient to prevent weight gains in the general population. The committee feels that it takes at least one hour of moderate physical activity daily in order to achieve this. This probably also suffices in adults to prevent moderate overweight to develop into obesity.

Other causes

While genetic factors play a part in the development of overweight and obesity, the influence of environmental factors appears to be of overriding importance. As yet, very few of the genes responsible for susceptibility to the development of overweight have been identified. The same is true of the part played by...
interactions between genes, as well as interactions between genes and lifestyle factors.

Little targeted research has been carried out into the influence of specific behavioural determinants and of environmental factors which underpin high-risk behaviour associated with the development of overweight (overconsumption and an inactive lifestyle). With regard to eating behaviour, it has been established that food preferences are often acquired at an early age and that preferences for energy-rich foods are easily acquired. In addition, research into eating behaviour and physical exercise has shown that many people are unaware of how much they eat and how little exercise they take. Individuals must therefore develop an adequate awareness of their own eating behaviour and patterns of physical exercise. This is an essential first step in the instigation of behavioural changes. Furthermore, interactions between parents and children, role-model behaviour by parents, and rules imposed during upbringing are major factors which can affect the development of overweight in children.

There is strong evidence that various physical, economic and sociocultural factors (the so-called 'obesogenic environment') prompt individuals to eat large amounts of food and to take little exercise. For example, various studies of children have found a link between the number of hours spent watching television and the development of overweight. There is a major correlation between the higher prevalence of obesity in population groups with a low socio-economic status and environmental factors which tend to impede healthy behaviour.

Effective preventive intervention strategies

An intervention strategy that can effectively prevent weight increase has yet to be devised. Nevertheless, the reported results of some short-term interventions involving schools in other countries reveal a slight beneficial effect on the prevalence of overweight in children. It is not known whether this is a short-term or long-term effect, however. The effectiveness of interventions which target environmental factors (in such areas as housing, transport systems, education, pricing and fiscal measures, and available foods) has also been too poorly studied to enable a verdict to be reached.

There has been scarcely any systematic research into the effectiveness of preventive interventions used in accordance with modern views on health promotion. This is based on a combination of interventions in the field of
information provision, regulations and environmental factors. This view dictates that the interventions be attuned to the specific behavioural determinants and environmental factors which underpin high-risk behaviour. The aim of the interventions must be both to increase the usual amount of daily physical activity and to reduce the energy intake. The development and implementation of such intervention programmes requires a broad coalition of actors, in which the local and national authorities, the industry, the health care system and the population each carry their own responsibilities.

Treatment

According to international guidelines, the primary aim of obesity treatment should be to achieve a long-lasting weight loss of about 10%. Even this relatively small weight loss can produce significant health gains. It is very important that also in the Netherlands a treatment protocol for the involved health care professionals is drafted.

Dependent on the amount of overweight involved and on the presence of comorbidity, one option is an integrated approach, aimed at bringing about changes both in terms of behaviour (diet and physical activity) and cognitions, in some cases in combination with pharmacological or surgical therapy. The only effective strategy for obese children appears to be behaviour therapy in groups, in which the parents also participate.

On the basis of strict selection criteria, individuals with extreme overweight are eligible for medicinal or surgical treatment. Surgical treatment may be the solution in some cases of extreme obesity. Both treatment strategies must be used in combination with a weight management programme. There have been favourable reports about both medicinal treatment and surgical treatment, based on weight loss and improvements in terms of health risk factors and quality of life. Data on long-term results is only available for surgical treatment.

The most important problem in current obesity treatment is that any weight loss achieved is not usually long-lasting. The suspension of treatment negates its effects. This does not mean that obesity is untreatable. What it does show is that the treatment was effective but that it was terminated prematurely. While there have been very few studies into the effectiveness of longer duration treatments (exceeding two years), some studies have described cases of long-lasting weight loss spanning periods of several years.
While the treatment prospects for obese patients have improved in recent years, it should be pointed out that the beneficial results obtained only apply to a limited group of patients and then only for the duration of their treatment.

Further research

Some research projects currently in progress may, in the future, provide important information relating to the prevention and treatment of overweight and obesity. In view of the complexity and severity of the obesity problem, however, further research is required in many subfields.

The committee expects that knowledge on the effective prevention and treatment of overweight and obesity will gradually increase. It does not expect scientific breakthroughs at short notice.
Ministers of the Dutch government asked the Health Council to address a number of questions regarding foods and dietary supplements with health claims. The questions raised related to the health benefits achievable by the use of such products, their safety, the differentiation between different types of claims, and the evidential basis for these claims. A Health Council Committee has addressed these questions.

**Health benefits**

Diet influences health; it is possible to obtain health benefits by consuming certain foods and dietary supplements. Vitamins and minerals, for example, prevent deficiency diseases. Energy intake influences the risk of obesity, and therefore has an effect on the risk of cardiovascular disease and diabetes mellitus. Dietary fats and fibres influence the risk of cardiovascular disease, and the use of folic acid by pregnant women reduces the likelihood of foetal neural tube defects. Under the present circumstances, the greatest public health benefits are likely to be achieved through the consumption of new or established products that utilise these already demonstrated effects of diet on health. Optimisation of the national diet depends at the very least on consumers having correct information. Producers, the Netherlands Nutrition Centre and the government, as well as dieticians and doctors all have a role to play in this regard.
Safety

Products with health claims are frequently enriched with “classic” nutrients. Enrichment is useful insofar as it results in more people consuming the recommended daily intake of a nutrient. Increasing intake to a level in excess of the recommended daily intake is generally pointless, and is therefore not a valid case for enrichment. Consumption should not exceed the safe upper limit of intake. The risk of such excess consumption is greatest where several products enriched with the same substance are used concurrently, and especially where supplements are concerned. By reference to the findings of the Food Consumption Surveys, it is possible to estimate whether and, if so, to what extent the enrichment of a given product is liable to lead to overdosing. The intention is that food is safe. Actual practice, however, shows that many foods, including some widely consumed products, can have undesirable effects. These effects may nevertheless be deemed acceptable if offset by significant positive effects. Market monitoring is desirable in order to highlight these sorts of issues.

Differentiation of claims

The law in the Netherlands allows foods and dietary supplements to be accompanied by “health claims”, defined as claims relating to the “promotion and maintenance of health”. Medical claims are those involving the “prevention, treatment and cure of disease”. These claims may be made only for medicines and are forbidden for foods and for dietary supplements. However, the Committee believes that there is no scientific or practical distinction between the “prevention of disease” and the “promotion and maintenance of health”. Hence, the boundary between medical claims and health claims is not clear. The same applies to the boundary between foods and medicines. Both may be capable of beneficially influencing disease risk factors, causing reduction of disease risks. And any intervention aimed at reducing a disease risk (to or towards zero risk) is at the same time aimed at disease prevention.

The ministers asked whether a claim regarding the reduction of a risk factor may legally be interpreted as a (lawful) health claim, rather than an (unlawful) medical claim. However, as indicated above, the Committee does not see a difference between health claims and prevention-related medical claims. A claim that a product influences a particular factor can give the impression that use of the product reduces the likelihood of developing a certain disease. If this impression is correct, it is better to explicitly state that effect. If this impression is
not correct, the claim is irrelevant and therefore misleading. Only explicit, specific and evidence-based claims regarding the prevention, and possibly the treatment, of diseases or conditions are of any value to public health. The prohibition of claims regarding risk reduction is an obstacle to ensuring that consumers are fully and correctly informed.

Nutrient content claims are statements such as “rich in ...” or “low in …”. Such claims can also easily give the impression that use of the product is healthy and reduces the risk of developing certain diseases. It is better that this impression be made explicit, that the diseases in question are specified, and that evidence is provided. Here as well the principle should rule that if a claim cannot be made explicit or supported by evidence, then it is irrelevant and therefore misleading.

**Evidential basis**

No general and precise guidelines can be provided for the assessment of claims. A group of experts should be given the task of reviewing all the research data relevant to a claim, taking account of the methodological quality of the studies, their duration and nature, and the consistency of the findings. A claim must always be supported by research involving human subjects and generally accepted scientific criteria must be followed. Along with being statistically significant, a claimed effect must be of sufficient practical significance. Because new scientific developments can invalidate a claim, it is important that claims be periodically re-assessed.

Health effects from foods or dietary supplements do not normally occur in everyone. Their occurrence depends partly on factors such as lifestyle, including the consumption of other substances, sex and other genetic factors. The reporting of a claim that does not specify the target group is incomplete and therefore misleading.

In the assessment of claims, account should be taken of any adverse effects that a product may have. It would improve the clarity of the system for the business community, the government and consumers if the same agency were responsible for assessing both the safety and health effects of foods and dietary supplements.
Exposure to electromagnetic fields generated by mobile telecommunication equipment is a growing source of concern in the population. Anxiety increases that such exposure may lead to adverse health effects. The Health Council of the Netherlands was asked by the Government, partly because of a motion of the Second Chamber of Parliament, what research might be performed in the Netherlands to obtain a better insight into possible health effects of exposure to electromagnetic fields. In this report the Electromagnetic Fields Committee of the Health Council makes proposals to this end.

In earlier reports the committee has given an overview of the scientific knowledge with respect to health effects of electromagnetic fields. On the basis of this understanding and an inventory of ongoing research, it indicates the most important gaps in knowledge and which questions should be answered first to meet public disquiet. The committee proposes various types of studies: *in vitro*, *in vivo*, human experimental, epidemiological and dosimetry and model studies.

**Centre of expertise**

Before discussing what research might be performed in the Netherlands, the committee strongly recommends to establish a Centre of expertise regarding health effects of electromagnetic fields. One of the tasks of this centre, that should have an academic setting, should be to combine and expand the knowledge that is presently available in the Netherlands within several relatively
isolated operating research groups. Furthermore it should coordinate research in the Netherlands, guard its broad outlines and gear it to the worldwide scientific developments. The Centre of expertise should also have a role is academic teaching activities on this subject. These tasks can only be realized if a coordinator is appointed with a broad knowledge of electromagnetic field issues.

**In vitro studies**

The committee recommends to perform *in vitro* studies in the Netherlands into the interaction of electromagnetic fields and chemical and physical agents. Especially in the working environment combined exposure frequently occurs. A better knowledge of its possible effects is very important.

**In vivo studies**

According to the committee it is not advisable at this time to make proposals for animal studies to be performed in the Netherlands. The most important questions for which this type of research is indicated, are being studied elsewhere.

**Human experimental research**

Health complaints are a major source of public anxiety and adequate data on the relation between such complaints and electromagnetic field exposure is virtually lacking. The existence of sensitive subpopulations cannot be excluded. Therefore experimental human studies are urgently needed. The committee proposes to focus on studies of subjective complaints, under the condition that the effects can be objectively established.

This type of research, that is of an experimental nature and takes place under controlled conditions, can very well be performed in the Netherlands. A small-scale study is currently being carried out. The committee recommends to expand the possibilities to perform this type of research in the Netherlands. In order to obtain a better understanding of possible causal relations it is essential that various exposure characteristics are being investigated, for instance field strength, frequency and pulse shape.

**Epidemiological studies**

The committee thinks it is important to investigate the incidence of adverse health effects in relation to the use of mobile telephones and living near GSM
base stations or radio and television transmitters in the Netherlands. A two tier approach is recommended:

- to perform an experimental epidemiological study into the occurrence of subjective health complaints in people living near GSM base stations. Also the effects of providing information and of monitoring should be assessed.
- to perform a large-scale cohort study into the relationship between electromagnetic field exposure and a variety of health effects, including cancer. Important requisites for such study are that the exposure can be quantified, that there is sufficient exposure contrast and that the study extends over a sufficiently long period of time. The most important variable should be the use of a mobile telephone, but also living near radio and television transmitters could be investigated. This study could be incorporated in cohort studies presently ongoing in the Netherlands. Alternatively, participation in studies being set up elsewhere could be considered.

The committee doubts the usefulness of studying the incidence of cancer and other diseases in people living near GSM base stations. The most important reason for this is that such people are exposed to only very low field strengths, also if these are considered relative to field strengths from other sources such as radio and television transmitters. Before proposals for this type of research should be requested, its feasibility should be investigated. In Germany such studies are currently being set up. The experiences gained with that could be used. These arguments do not apply to radio and television transmitters. Therefore these have been suggested as sources to be included in the cohort study mentioned above.

**Dosimetry and model studies**

Current exposure limits have been drawn up for so called far field exposures. In practice, however, exposures in the near field increasingly occur. This is especially the case with the use of a mobile telephone, because the antenna of such devices are close to the body. The committee therefore thinks that studies should be performed in the Netherlands how the basic restrictions can be translated into reference levels under near field exposure conditions. This means that a better insight is necessary into the relation between the SAR and easily measurable quantities such as the electric and magnetic field strength and the power density of the electromagnetic field. Also more knowledge is needed on the interaction of electromagnetic fields and biological structures.
There is also a need for adequate modelling of the fields generated by an antenna and for research into modelling of the known effects of electromagnetic field exposure (the heating in the radiofrequency range).

In order to support the dosimetry of especially the epidemiological studies the committee recommends to develop suitable measuring devices that can register field strength data over a wide frequency range in the living and working environment over a set period of time.

The committee finally makes a plea to establish a specialized group of experts that should be responsible for the dosimetrical aspects of the various studies to be performed in the Netherlands. This will prevent that such highly specific expertise has to be developed in each individual research group. Also the dosimetry can be performed by the same groups of experts, which increases the quality of the studies.

**Further recommendations**

The committee thinks it is of the utmost importance that collaboration be established between researchers from the Netherlands and other countries. One of the reasons being to create the possibility to qualify for additional financing of studies in the Netherlands from international sources, such as the 6th Framework Program of the European Union.

**Time frame**

In the request for advise the time scheduling of the studies is asked for, especially within the context of the WHO’s International EMF Project. The final report of this Project with respect to radiofrequency electromagnetic fields is scheduled for the end of 2004. It is not realistic to expect that results from studies to be performed in the Netherlands according to the present proposals will be available by then.

The committee stresses, however, that also the WHO Project cannot give the definite answer to the question whether exposure to electromagnetic fields may lead to adverse health effects. Especially the question whether long-term exposure to the fields generated by the antennas of mobile telephones and their base stations may result in disease needs a longer period of observation than until 2004. Therefore also after completion of the WHO International EMF Project the possible occurrence of health effects should be constantly monitored. The studies proposed in this report are aimed at that. The committee does think that, should the proposals from this report be adopted, it is necessary that funds are made
available at short notice, in order to allow the tendering of research proposals and to perform the studies. This is important in order to join in with the international research efforts. Additionally, research in the Netherlands is of importance because of its high social relevance and the concern about possible health effects of mobile telecommunication.

**Organization**

The committee proposes to accommodate the research formulated in this report with the Netherlands Organization for Scientific Research (NWO) and the Netherlands Organisation for Health Research and Development (ZonMw) with respect to the biological subjects, and with the Foundation for Technical Sciences (STW) with respect to the technical subjects.
Benchmark dose method: health-based recommended exposure limits in new perspective


Exposure to a chemical via air, water or food can result in the impairment of health, depending on the degree of exposure and the toxicity of the substance. Health-based recommended exposure limits for a substance correspond with the highest estimated dose or concentration that does not lead to health impairment.

To support the implementation of policy on industrial safety, environmental management and food safety, the Health Council derives such limits for specific substances. The Council also studies the methods employed to derive recommended exposure limits, and from time to time it advises modifying these methods to bring them into line with the latest developments in scientific knowledge.

This document, drawn up by the Health Council’s Committee on the Derivation of Health-Based Recommended Exposure Limits, forms one such methodological advisory report. It discusses the use of the ‘benchmark dose’ or BMD method in deriving health-based recommended exposure limits. This method is an alternative to the approach generally employed in the Netherlands and elsewhere, in which either animal experiments, studies with volunteers or epidemiological research are used to determine the highest level of exposure which does not lead to adverse health effects (the No Observed Adverse Effect Level, or NOAEL). An ‘uncertainty factor’ is then applied to allow for the differences between experimental animals and humans, differences in sensitivity between human individuals, and research data deficiencies. The resulting exposure value becomes the health-based recommended exposure limit.
Background

The reason that an alternative is being sought lies in the shortcomings of the NOAEL method, the most important of which is that an NOAEL value strongly depends on the quality of the available research data. The less precise this data is, the larger the corresponding NOAEL value tends to become. However, for the purposes of public health protection one would prefer such data imprecision to imply a lower NOAEL value rather than a higher one. Evaluation studies have shown that, in practice, exposure to levels equal to (or even below) the NOAEL does not rule out the occurrence of adverse health effects. The fact that health-based recommended exposure limits do indeed provide public health protection is due to the magnitude of the uncertainty factors which are used to derive the recommended exposure limit from the NOAEL. The way in which such factors are determined is rather ad hoc.

This last argument also demonstrates why an apparently simple approach ought to be replaced by a mathematically and statistically complex one. The simplicity of the NOAEL method conceals considerable uncertainties, which are explicitly addressed in the BMD method. The BMD method can therefore yield health-based recommended exposure levels having a lower inherent uncertainty than the figures generated using the NOAEL approach.

The BMD method

The BMD method sets out to analyse the data on the effects of a chemical on animal or human health in order to determine, as accurately as possible, the relationship between a given exposure level and the likelihood of its detrimental effects (the so-called response). The statistical uncertainty to which this data is invariably subject is incorporated into the calculations. The figures are then used to yield a ‘benchmark dose’ or BMD: this is the dose which corresponds with a given statistical likelihood of health impairment in the exposed population—for instance, 1 per cent or 10 per cent. The BMD is then divided by an uncertainty factor to yield a health-based recommended exposure limit.

As has already been mentioned, the BMD method takes better account of research data uncertainties than does the NOAEL method. Moreover, the NOAEL is by definition one of the experimental doses applied, while the BMD is a quantity derived from all experimental values. Finally, the BMD method also holds out the prospect of obtaining information about the risks associated with exposure exceeding the health-based recommended exposure limits.
In 1996 the Committee recommended that it be investigated whether these theoretical advantages also existed in practice. In the Netherlands, the Ministry of Housing, Spatial Planning and the Environment and the Ministry of Social Affairs and Employment commissioned the TNO Nutrition and Food Research and the National Institute of Public Health and the Environment to carry out this research. Outside the Netherlands, too, useful experience has been gathered on the BMD method, stimulated in particular by the US Environmental Protection Agency. The Committee has assessed the findings of this research and now presents the following conclusions and recommendations.

Feasibility of the BMD method

Research in recent years, both in the Netherlands and elsewhere, has shown that the BMD method offers clear and tangible advantages over the existing NOAEL method. The Committee is of the opinion that if these advantages are to be fully exploited, the protocols for toxicological studies should be modified. It also notes that comparatively little attention has so far been given to the uncertainty factor that must be applied to the BMD in order to yield a health based recommended exposure limit. Although this aspect was outside the scope of its remit, the Committee recommends further study of the extrapolation from BMD tot exposure limit.

Another point requiring closer attention is the choice of a model function to describe the form of the dose-effect (or dose-response) relationship. These functions are currently still strongly determined by statistical considerations. The Committee holds that it would be desirable to strengthen the biological basis of this choice. The same applies to the choice of the degree to which an effect is deemed no longer not to impair health. For example, is a 5 per cent weight gain in the liver with respect to the average liver weight in a non-expose population evidence of damage to health, or would 10 per cent still be compatible with good health? This choice should be made on biological and toxicological grounds wherever possible. However, this is easier said than done. The Committee therefore indicates a route by which, for the time being at least, this choice can be made on the basis of pragmatic considerations.

Notwithstanding the need for its further development, the Committee considers the BMD method to be a useful technique for the derivation of recommended exposure limits. Where toxicological data makes its application possible, the Committee prefers the BMD method above the NOAEL approach. The BMD method yields improved foundations for health-based recommended exposure limits and, when deriving these limits, it curtails dependency on

Benchmark dose method: health-based recommended exposure limits in new perspective89
uncertainty factors that have been arrived at on the basis of qualitative considerations. The Committee recommends that the Dutch government accept the derivation of recommended exposure limits using the BMD method as the basis for limit values laid down in law or governmental policy.

**Estimating effects**

The Committee is less sanguine about the prospects of estimating the effects of exposure exceeding the health-based recommended exposure limit. It considers that considerable uncertainties are attached to such estimates, and that they should therefore be used with extreme caution in concrete cases of exposure to toxic substances. Given the need for such estimates, the Committee recommends that the government support further research into the reduction of these uncertainties.

**Additional advice**

In order to further develop the BMD method and its application in determining recommended exposure limits, the Committee considers additional advice to be required in three areas in particular:

**Uncertainty factors**

The Committee recommends that the Health Council assess the customary values of the uncertainty factor and new approaches for describing this factor. It considers that an international panel of experts is called for.

**Protocol development**

The Committee notes that existing protocols for toxicity studies are not well matched to BMD methodology, although their application does not make it impossible. It recommends that steps be taken to modify the protocols accordingly. If the Dutch government adopts the Committee’s views on the usefulness of the BMD method, it should also stimulate discussion of this matter at OECD and EU level.
Choice framework for BMD parameters

The BMD method demands that three choices be made: the statistical likelihood of an effect underlying the determination of the BMD; the dividing line between an effect size deemed to be benign and one deemed to be non-benign; and the choice of a model function with which to describe the relationship between dose and effect. As things stand, these choices have to be made and justified on a substance-by-substance basis. The Committee considers it desirable that this reasoning be carried out within a framework of selection criteria. It proposes that the Health Council or other authoritative body initiate the creation of such a framework, preferably at an international level.
In 1990, a Health Council advisory report was published on the harmfulness of exposure to environmental tobacco smoke (‘passive smoking’). We now know much more than we did then. This was sufficient reason for the President of the Health Council to appoint a committee, with the task of assessing the current level of knowledge concerning the damage caused to public health by passive smoking. In particular, the Committee should focus on the extent to which such damage can be quantified. This advisory report presents the result of its deliberations.

In the Committee’s view, we now have a much better understanding of how inhaled environmental tobacco smoke can damage the body’s cells and organs than we did thirteen years ago. Furthermore, many well designed epidemiological studies have been conducted into various harmful effects of passive smoking since then. Many meta-analyses (a quantitative type of literature survey in which the results of different epidemiological studies are combined) have also been carried out in the intervening years. The Committee has drawn up a list of links between the damage to health and passive smoking that have been investigated in the intervening years. It evaluated the characteristics of these links in terms of causality and, where possible, strength. The latter involves the so-called relative risk. This is the risk of exposed individuals acquiring a given disorder, divided by the corresponding risk in non-exposed individuals. The
principal conclusions, which are applicable to an average exposure to
environmental tobacco smoke, are as follows:

- There is sufficient evidence that passive smoking can cause lung cancer. The
  increase in risk is approximately 20 percent.
- There is insufficient evidence that exposure to environmental tobacco smoke
  increases the risk of other forms of cancer.
- It has been convincingly shown that passive smoking leads to an increased
  risk of cardiovascular diseases. The increase in risk is 20 to 30 percent.
- Women who are active or passive smokers during pregnancy give birth to
  children with lower average birth weights and shorter average birth lengths.
  The increase in risk is approximately 20 to 40 percent.
- It is estimated that exposure to environmental tobacco smoke doubles the
  risk of sudden infant death syndrome (in other words, the increase in risk is
  approximately 100 percent).
- There are indications that both prenatal and postnatal exposure to
  environmental tobacco smoke adversely affect certain cognitive abilities
  (such as language capacity and learning capacity) and behavioural
  characteristics (such as activity and concentration capacity) of children. The
  true extent of this problem cannot yet be reliably assessed.
- Passive smoking leads to an increased risk of infections, or more severe
  infections, and to a higher frequency of respiratory tract symptoms in
  children with or without asthma. The increases in risk vary from
  approximately 20 percent to approximately 50 percent, dependent on factors
  such as the effects investigated, the nature and extent of exposure and the
  age of the children in question.
- There are indications that passive smoking increases the risk of chronic
  respiratory tract complaints in adults (especially in asthmatics).

The Committee went on to consider the significance of these relative risks in
terms of the annual number of cases of illness and death in the Netherlands that
can be attributed to passive smoking. Any such assessment would require
information on the incidence rates of the associated disorders (and resultant
deaths), broken down into age, sex and smoking status. It would also require
prevalence rates for exposure to environmental tobacco smoke, broken down into
age, sex and location. The Committee has found that many of the requisite rates
are not directly available. Most of the data can probably be located, but this will
involve further research. The Committee feels that it is important for this
research to be completed. Its reasons include the need to monitor measures introduced to cut down on passive smoking.

The Committee believes that figures from the US make it possible to reach a verdict regarding the order of magnitude of the burden of disease and death involved. It is estimated that, each year, passive smoking in the Netherlands causes:

- several hundred deaths from lung cancer
- several thousand deaths from cardiovascular diseases
- about ten cases of sudden infant death syndrome
- several tens of thousands of cases of respiratory tract disorders (in varying degrees of severity) in children

These rough estimates do not characterise the full extent of the harmfulness of passive smoking. Accordingly, the risks of cardiovascular diseases do not relate to mortality alone, they also include morbidity. Harm resulting from prenatal exposure to tobacco smoke also has to be included. The associated smell and irritation also cause widespread annoyance.

Importantly, this is a burden of disease and death that can be curtailed. Reducing the exposure of non-smokers to environmental tobacco smoke will cut the incidence of disease and death in this group. For some disorders, such as lung cancer, the risk will decline very gradually. In other cases, health gains will be achieved almost straight away or within a short space of time. This would seem to apply to some cases of heart attack and to various respiratory tract complaints.

A tightening-up of the Tobacco Act should further reduce levels of passive smoking in the public domain. However, smoking at home while others (particularly children) are present, still poses a considerable problem. In this connection the Committee sees as a task for physicians, obstetricians and the staff of post-natal clinics. It feels that these individuals should warn people frequently and clearly about the hazards of passive smoking. Consideration should be given to the inclusion of such instruction in the basic job description of individuals working in child healthcare.
Health and the environment: monitoring options


Request for advice and Committee

On 12 May 2000, the government ministers with responsibility for Health, Welfare and Sport (VWS) and Housing, Spatial Planning and the Environment (VROM) asked the Health Council to identify ‘the conditions to be met by monitoring programmes used in support of policy in the area of environment and health’. They cited the following range of situations which lend themselves to monitoring: environmental incidents, perceived health problems which citizens ascribe to local environmental factors, health assessments of various policy scenarios and in tracking trends in the repercussions of environmental policy in order to protect public health.

In response to the Ministers' requests, the President of the Health Council appointed a committee on 9 October 2001. In drawing up its report, the Committee had access to the results of interviews conducted with thirty experts. It also had at its disposal a list of relevant environmental factors, indicators and registration systems, which had been prepared at the Health Council's instruction. Finally, it incorporated the findings of the Invitational Conference on Small Area Health Statistics, which was organised by the Health Council.
Monitoring

In this advisory report, the word 'monitoring' is taken to mean the periodical measurement, analysis and interpretation of indicators for environmental factors which are relevant to health, or for health problems which can be ascribed to environmental factors. There are multitudes of environmental factors. Accordingly, the Committee has limited the scope of this report to the monitoring of chemical and physical agents. Biological environmental factors, such as biogenic allergens and toxins, have been given no further consideration in this report. The same applies to the monitoring of external safety risks.

The three monitoring applications addressed by the Committee were:
- surveillance of exposure to environmental factors which are known to be hazardous
- identification of possible health effects caused by suspect environmental factors
- verification of exposure situations or health problems that are a source of concern.

Criteria for monitoring

The first of the ministers' requests concerned the conditions to be met by monitoring programmes used in support of policy in the area of environment and health.

In response to this request, a set of assessment criteria has been developed. These are summarised in the following box.

Criteria for the social relevance of environmental risks:
- Understanding of the relationship between exposure and effect
- Severity and scope of the problem

Criteria relating to the objectives of monitoring:
- Objectives of risk surveillance:
  - verifiability in terms of policy or standards
  - intervention perspective
- Objectives of risk identification:
  - social concern
Methodological criteria:
• Measurability / reliability
• Interpretability

Criteria for measurement and registration programmes:
• Representativity and completeness
• Extent of geographical coverage
• Sufficiently detailed scaling level
• Continuity / periodicity

## Current monitoring programmes

The second question concerned the practicality of current measurement and registration programmes in terms of answering questions about the influence of environmental factors on health.

After taking stock of the relevant environmental factors, indicators and registration systems, it was found that, in their present form, few of the Dutch monitoring programmes are fully effective in identifying and assessing the health effects of environmental pollution. On the one hand, environmental factors have relatively minor effects on health. This makes it difficult to detect the effects in question, which are often non-specific in nature. On the other hand, there is little or no harmonisation between the various monitoring activities.

Those programmes that are of practical value in the monitoring of exposure indicators are the Dutch National Air Quality Monitoring Network and the five-yearly study of dioxins and polychlorinated biphenyls (PCBs) in breast-milk conducted by the National Institute of Public Health and the Environment (RIVM). Those concerned with the monitoring of health indicators are the Netherlands Medical Registration System for hospital data, the Cause of Death register and the Dutch Cancer Registration System.

The major limitations of most health registration systems are their coarse-meshed nature (especially in geographical terms), the fact that many are not up-to-date and that they are not accessible for secondary analyses, partly because of data protection legislation.

## Linkage of monitoring programmes for environment and health

The members of the government also asked the Health Council to indicate whether the linkage of current monitoring programmes for environment and health
health would have any added value in terms of providing answers about the
effect of environmental factors on health.

Only under certain conditions can the linkage of environmental and health data elucidate the causal relationships between exposure to environmental factors and health problems.

When it comes to specific questions with a clear public-health interest, environmental and health registration systems can be linked on an ad-hoc basis, provided that this is done at an adequately detailed scaling or aggregation level, preferably at the postcode level. This approach is of practical use in surveillance of the health effects of specific exposure situations, in answering questions in the event of concern about locally elevated rates of cancer or congenital anomalies and in providing answers for scientific research into cause and effect relationships. This requires a privacy procedure that can be quickly completed.

Studies of this kind are also described as ‘ecological’. However, conclusions about policy can only be drawn on the basis of research into the likelihood of a causal relationship existing between health effects and exposure to the environmental factors in question. ‘Semi-ecological’ research (in which aggregated measures of exposure are linked to individual health data and confounders) is very promising in this regard.

To improve its ability to interpret any associations between exposure to environmental factors and health problems, the Committee urges that, in future, health registration systems include more information on general risk factors, such as lifestyle (e.g. smoking), socioeconomic status and profession. This would then make it possible to adjust for these potential confounders at individual level. Where this is not yet the case, geographically aggregated data on smoking and socioeconomic status from other sources can also be used.

**Improving and supplementing current registration programmes**

Finally, the ministers asked the Health Council to identify the modifications required to increase the practical value of currently measured and recorded data, as well as the supplementary forms of monitoring required.

The following list of suggestions put forward by the Committee cannot be regarded as exhaustive.
Environmental measurement programmes

Environmental measurements should mainly be taken in places where a lot of people could be exposed to relevant concentrations. For this reason, the Committee recommended that the Dutch National Air Quality Monitoring Network be supplemented by taking air measurements at traffic junctions in housing estates. More specifically, they propose that the use of PM\textsubscript{10} as an indicator of inhalable particulates should be supplemented by measurements of PM\textsubscript{2.5} or even finer particulates. The Committee also urges that there should be a more systematic monitoring of contaminants in food and of contaminants in the indoor environment of newly-built houses.

Since people spend the vast majority of their time indoors, the Committee recommends that a study be carried out in the near future into the extent of exposure to environmental factors indoors, particularly nitrogen dioxide, volatile (and semi-volatile) and semi-persistent organic substances, and asbestos. More information is also required concerning the numbers of asbestos fibres in tap water after it has passed through asbestos-cement piping. The results of such a study could, if necessary, provide the basis for the development of an indoor-environment monitoring network to identify trends in exposure.

In order to monitor the risks associated with long-term exposure or to establish the exposure of the general population, model-based calculations must be combined with measurements. This applies not only to air pollution but also to physical agents such as sound and electromagnetic fields. In order to provide further support for the current national noise model, it is recommended that a more systematic measurement of noise load in the domestic environment be carried out. Calculation of the field strength per source is sufficient for the monitoring of exposure to electromagnetic fields produced by outdoor sources.

Biological monitoring programmes

For several years, the Surveillance Programme Man, Food and Environment of the Inspectorate for Health Care provided a good basis for monitoring the body burden of persistent environmental contaminants in blood or urine. With the cessation of the collection of blood and urine samples via municipal health services, we have lost a cost-effective means of collecting material and background information in a representative random sample of the adult population. The Committee feels that it is important to look for alternatives to

* PM\textsubscript{10} and PM\textsubscript{2.5}: particulate matter, particles with an aerodynamic diameter of less than 10 or 2.5 µm respectively
this programme. The monitoring programme for contaminants in breast milk still offers a good basis for monitoring the body load of persistent* compounds. A welcome extension to this programme is the inclusion of bromine compounds that are used as fire retardants. Because of their persistence, these compounds are increasingly present throughout the environment.

It would also be desirable to set up a specific biological monitoring programme for high-risk groups, such as new-born babies. If umbilical cord blood or heel stick samples are systematically collected and stored, this would facilitate studies into the significance of contaminants such as persistent organic compounds or heavy metals in the occurrence of developmental disorders. With this in mind, the Committee recommends that the possibility of keeping systematically collected human tissue samples in long-term storage be examined.

Before new biomarkers are incorporated into a biological monitoring programme, research is needed to expand the arsenal of instruments available for biomonitoring purposes. In this context, the development of exposure biomarkers would be particularly useful, using methods that have proved their worth in the field of occupational toxicology. It is not expedient to develop monitoring programmes for effect biomarkers, while their usefulness and expressiveness remain unproved. However it is important to carry out studies to validate current methods of measuring specific effect biomarkers for additional substances, such as those for protein adducts and possible DNA adducts, or other indicators of genotoxic damage. In doing so, consideration should be given to the relationship between these indicators and damage to health.

**Health registration programmes**

The Committee feels that people generally have overblown expectations with regard to the monitoring of health effects resulting from environmental pollution. By no means all of the symptoms or disorders which could be related to environmental factors or which are a cause of concern are systematically recorded. Furthermore, recording this information does not always lead to a solution, for instance when the data are not available at the required scaling level. Disappointment can be avoided if those involved are first given an explanation of the limitations of monitoring programmes.

In more specific terms, the Committee takes the view that health registration systems must be more accessible for the purposes of secondary analysis. The need to protect people’s privacy demands that efficient privacy procedures be

* persistent: poorly biologically degradable and, as a result, accumulating in the environment
developed. One way in which this could be done is to make prior agreements concerning standard analytical procedures.

The monitoring of health indicators in high-risk populations can have added value. High-risk populations can either be groups with a high level of exposure (e.g. in certain underprivileged neighbourhoods) or groups with a high level of sensitivity, such as children.

There is concern about the possible toxic effects on the reproductive system of materials such as persistent organic compounds. Accordingly, it is also important that a single, easily accessible and up-to-date national registration system for congenital anomalies be created from the various existing registration systems. Ideally, this registration system would be expanded to include data on developmental disorders which are not recorded until a considerable period of time after birth. Partly for this reason, the Committee recommends that youth health care registration systems be further harmonised and computerised. Ideally, other reproductive disorders (e.g. subfertility) should also be added to such a national monitoring system.

For some questions, such as those concerning perceived risk or perceived health, there would be little sense in consulting existing registration systems. For this purpose, it would be better to collect new data through targeted research. It might therefore be useful to collect data on people’s state of health, the perceived nuisance and relevant determinants at regular intervals (e.g. every five years), at the level of the individual. This will depend on the specific situation and population concerned and the availability of suitable indicators. The ‘Local and National Monitor’ project run by the Dutch Association of Municipal Health Services and RIVM is very promising in terms of following national trends in self-reported symptoms and disorders in relation to the environment. The questionnaire used in this health survey has a separate module, entitled 'environment', which contains questions on health and environment. It is therefore of the utmost importance that all municipal health services actually implement this module in their health survey.

**Standardisation and evaluation**

In the interests of comparing data, in terms of time and place, it is essential that the methods and techniques used should be better harmonised at national level. These should also be standardised at international level, as far as possible. Accordingly, it is recommended that the indicators and instruments developed by the WHO be used wherever possible. This simplifies the process of making local,
national and international comparisons, as seen in the framework of the European Directives on air pollution and noise.

Dependent on the current scientific situation or on indicator trends, new environmental factors or health indicators can be added to existing programmes or the monitoring of specific indicators can be suspended. It is therefore recommended that monitoring programmes be regularly evaluated. Naturally, cost-benefit ratios have an important part to play here. Monitoring provides only a part of the information required for risk management or health protection.

Meta information systems

Monitoring by means of measurement and registration programmes is just one element of a knowledge-based system. In general, meta information systems, such as the reports State of the Environment and Environmental Outlook (prepared by RIVM for the Dutch government) are better suited to answering questions about the influence of environmental factors on health. These documents monitor the scientific situation, on the basis of measurement data and literature.

Three types of expertise networks are required to compile and open up meta information, dependent on the type of monitoring involved (surveillance, identification or verification of risks):

• a knowledge and information centre, which collects and provides information on the risks of environmental factors which are known to be hazardous
• a platform for risk identification, which focuses on identifying presently unknown health risks from environmental factors and on developing novel insights
• an expertise platform for health and environmental monitoring, that exists primarily to verify exposure situations or health problems (or clusters thereof) wherever there is concern.

As far as the latter is concerned, the Invitational Conference on Small Area Health Statistics revealed that there is clearly more support for an expertise platform than for a single centre in which all health and environmental registration systems would be gathered together. Dependent on the specific question being posed, this platform would facilitate efficient cooperation with experts in the various fields involved, and with experts in the field of health registration systems, environmental registration systems and the registration of
confounders. It would also make it possible to coordinate different studies with one another.

Conclusion

All things considered, the Committee concludes that, following testing against a set of core criteria, few monitoring programmes are fully effective in the surveillance and identification of the health effects of environmental pollution.

It takes the view that data protection legislation, which usually prevents the linking of databases, poses significant limitations on the use of health registration systems. In that connection, the Committee recommends that, when evaluating the Personal Data Protection Act, consideration be given to problems associated with the provision, linkage, analysis and presentation of health data at a low aggregation level. Furthermore, health registration systems generally do not contain or provide any information about personal risk factors which might disrupt a possible relationship between environmental and health indicators. The Committee therefore concludes that people generally have overblown expectations with regard to the monitoring of health effects resulting from environmental factors.

In view of the complexity of research involving aggregated databases, the Committee feels that it would be useful to establish an expertise platform for health and environmental monitoring, which could facilitate research of this kind. The Committee also feels that it would be useful to identify other possible health risks of environmental factors (e.g. from the literature) in a more systematic way than has hitherto been the case.
Environmental Health: Research for Policy


Issue addressed and approach

What knowledge are we missing about the way our surroundings influence our health? And what research is required to fill the holes in such knowledge? These questions were posed by the Netherlands’ State Secretary for Housing, Spatial Planning and the Environment when asking the Health Council to produce this report. Behind the questions was a wish to obtain the research data necessary to more effectively protect public health against harmful environmental factors and to allay unfounded concerns about environmental factors. The State Secretary was chiefly interested in the effects of physical factors, such as substances in the air, the water and the soil, ionising radiation, electromagnetic radiation and fields, and noise. Every one of these factors was referred to in the Action Plan Environmental Health: Implementing more powerful policy, presented to the Lower House of the Dutch parliament in 2002. The Action Plan Environmental Health also highlighted the importance of research into risk perception and risk communication.

To formulate a response to the State Secretary, the President of the Health Council sought input from both Council members and external experts that were consulted individually and invited to air their views at a working conference. This report has been drawn up on the basis of the feedback received.

The State Secretary asked the Council to put forward and assess subjects regarding promising fields of research. However, scientific research tends to
produce isolated puzzle pieces rather than an immediately coherent picture. If research is to offer practical support in the formulation of policy, it is necessary to determine which puzzle pieces go where and to sketch in the gaps in the picture—a process known as knowledge synthesis. As well as identifying topics warranting further investigation, this report therefore also indicates the fields where synthesis is desirable with a view to aiding the development of environmental health policy in the relatively short term (e.g. through the preparation of a report by the Health Council or some other body).

**Health and the environment**

The report begins with a general examination of the relationship between health and the environment. Less than a century ago, environmental factors such as polluted air and water were major causes of illness and death. Since then, adverse environmental effects on public health have been greatly reduced by action in the fields of environmental management and health care. The problems we face today tend to involve the combination of environmental influences with socio-economic and lifestyle factors, aggravating existing medical conditions and impairing the quality of life. When confronted by such problems, it is difficult to determine where one can most effectively intervene in order to reduce the health risks associated with our surroundings. In this report the Health Council advises the State Secretary not to focus exclusively on research that offers the prospect of short-term benefit, but also to promote fundamental research that will be valuable in the longer term. In this way, sustainable solutions can more easily be achieved.

Government policies aimed at enhancing the quality of our surroundings require coordination between various policy domains; improved public health can be achieved only through inter-sector collaboration. Such collaboration should not be confined to the public health and environmental policy domains (as occurred during the realization of the *Action Plan Environmental Health*), but should also embrace fields such as nature management, transport and the economy.

**Themes**

The background to the *Action Plan Environmental Health* and hence to the State Secretary’s request for advice was the consensus among Europe’s environment and health ministers that public policy had tended to neglect the influence of the environment on public health. There was also a consensus that there was a lack
of both knowledge and initiatives capable of effectively controlling the health risks associated with environmental factors. This has led to increases in research efforts across the EU. This report does not provide a comprehensive overview of such ongoing research. The research and knowledge synthesis initiatives proposed are intended to complement the work already being done in the Netherlands and elsewhere.

The report considers proposals for research and advice linked to nine themes:

- The quality of the human environment
- Chemical substances
- Noise
- Non-ionizing electromagnetic radiation
- Air pollution
- The indoor environment
- Combined exposures
- Risk perception and risk communication
- Monitoring

For each theme, the report assesses the extent to which knowledge regarding the seriousness and extent of the health effects is lacking and the level of public concern regarding the possible health detriment. The potential for each proposed research or synthesis activity to contribute to greater understanding of the health risks is then discussed, along with the short-term feasibility of each proposal.

The quality of the human environment

The report treats ‘The quality of the human environment’ as a general heading for a number of related topics. The quality of the human environment is influenced by numerous factors, between which the interactions are manifold. Consequently, it is not currently possible to quantify the health implications of the quality of our immediate surroundings. Nevertheless, while warning that it will take time to secure results, the report stresses the importance of research into this complex of factors and into ways of measuring the influence of this complex.
Chemical substances

The heading ‘Chemical substances’ covers issues relevant to the licensing of new substances and to the assessment of risks associated with existing substances, particularly those that are found in our living environment. Much work remains to be done in this field, since little or nothing is known about the significance of many substances to public health. The report emphasizes the potential benefits of research into the application of molecular-epidemiological methods designed to yield information about exposure to, and the impact of, substances in our living environment. A combination with genome research (genomics) offers the prospect of greater insight into the toxic effects of chemical substances.

Noise

A significant proportion of the Dutch population is annoyed or seriously annoyed by noise from neighbours, road, rail and air traffic, and industrial sources. The report focuses particularly on traffic noise and industrial noise. Gaps are identified in scientific knowledge regarding the relationship between cardiovascular disease and exposure to noise and regarding the general health implications of sleep disturbance associated with nocturnal noise. The report also suggests that more research is required into the way noise in domestic, school and recreational settings affects health and children’s short-term and long-term performance. Research into this topic is currently in progress, some of it under the European umbrella.

In view of the number of people exposed to and affected by noise, research into the effectiveness and efficiency of exposure reduction methods is also considered important.

Non-ionizing electromagnetic radiation

The possibility that mobile telephones or high-voltage power transmission may have public health implications is regularly aired in the media. The principal alleged culprits are radio-frequency radiation and the electromagnetic fields associated with power lines. As previously recommended by the Health Council, a European epidemiological research initiative is currently underway with a view to obtaining additional information. The report suggests that further action should be deferred pending publication of the results of this research. Nevertheless, the Council does recommend a survey of exposure to fields
generated by high-voltage power lines and electric equipment, as well as epidemiological research into the prevalence of leukaemia associated with such exposure. The State Secretary is warned, however, that such research is difficult, should be considered only in the context of international cooperation and cannot be expected to provide conclusive results in the short term.

Another topic addressed by the report is the effect on the immune system of ultraviolet radiation in sunlight and from sun beds. The Council’s view is that the time is ripe for a re-assessment of scientific knowledge in this field. Evaluation of extant research data on the protection against skin cancer offered by sun creams is also considered worthwhile.

Air pollution

One of the main causes of atmospheric pollution is the combustion of fossil fuels, particularly for transport purposes. Such pollution causes serious decrements in public health. Fine particulate materials, nitrogen oxides and ozone are of particular importance in this context. However, there is only partial knowledge concerning which pollutants or combinations of pollutants are detrimental to health and under what circumstances. The report therefore underlines the importance of research in this field and draws attention to the research already in progress, where Dutch researchers are also involved. It is expected that the results of such research will in due course enable the scientific community to advise the government with regard to its policies on air pollution.

Unpleasant odours are also a form of pollution of the outside air. While typically localized, odorous emissions can have a significant influence on the quality of the surroundings for those who live in affected areas. Although little additional evidence has come to light in recent decades regarding the relationship between odour, odour-related nuisance and health problems, the Council believes there to be scope for a synthesis of the published information.

The indoor environment

The theme ‘The indoor environment’ covers air quality within the home. The air we breathe in our own homes is generally more polluted than the immediate exterior atmosphere. The sources and causes of indoor pollution are well known: building materials, soft furnishings and furniture upholstery, cooking, and oxygen consumption and the production of carbon dioxide by the occupants. Yet, despite this knowledge, research indicates that little has been achieved in terms
of reducing the negative influence that domestic pollution has on public health. The report therefore recommends the compilation in the short-term of a scientific basis to facilitate the development of a strategic vision for improvement of our indoor environments, particularly the home environment.

The report also suggests that the situation in school buildings should be considered. It is conceivable that poor air quality in the school environment, possibly in combination with other environmental factors such as noise, could have an adverse effect on academic performance. However, little research has been done in this field.

Combined exposures

In practice, people are not exposed to an isolated environmental factor, such as a particular insecticide or a particular form of radiation. Exposure always involves several factors simultaneously or subsequently—different forms of air pollution, for example, or air pollution together with noise, or benzene both in the workplace and in the hobby room at home, etc. Despite this, we know much less about the significance of exposure to combinations of factors than about the effects of exposure to individual factors. The report accordingly highlights a number of topics that are felt to warrant further investigation: methods of risk assessment and, more fundamentally, the roles played by individual sensitivity and socio-economic circumstances in the occurrence of health effects. The State Secretary is advised that knowledge synthesis would be valuable for the assessment of ways of measuring health impairment, since measures of impairment are particularly relevant in the context of compound exposure.

Risk perception and risk communication

The public’s view of the health risks associated with a particular environmental factor is often very different from that taken by experts or the government. Given the divergent perceptions of risk and risk assessment that exist in society, the report would like to see more done to promote proper risk communication. Risk communication is defined as a two-sided process involving interaction between the government and the public (or between different non-governmental stakeholders) where there is the exchange of information concerning risk and value judgements. Through such a process, it is hoped that a common context can be created, within which appropriate value can be attached to estimates of environmental risk factors. The report holds that research into the effectiveness
of risk communication methods is urgently required and that there is a need for
the synthesis of knowledge in this area.

Monitoring

The report does not address the theme of monitoring because the Health Council
has very recently published a report entitled Gezondheid en milieu:
mogelijkheden van monitoring (Health and the environment: monitoring
options), in which detailed consideration is given to the development and the role
of monitoring systems.

Taking action

The report does not provide a list of proposals that can simply be picked up in
sequence. Rather, it makes proposals that are intended as a basis for a strategic
research programme that should tie in with international activities, in particular
at the EU-level, and to which researchers could lend their support. The report
calls for the promotion of a durable knowledge structure where fundamental
research is accorded proper importance. It is envisaged that such a structure
would be formed by researchers within universities and research institutes, such
as the Netherlands Organization for Applied Scientific Research (TNO) and the
National Institute of Public Health and the Environment (RIVM). The
Netherlands Organization for Scientific Research (NWO) is perceived as the
obvious supervisory body for the proposed strategic programme, and the
Netherlands Organisation for Health Research and Development (ZonMW) for
the applied research programme. NWO has adequate and established procedures
for assessing the quality of research proposals and testing them against a
strategic programme. Given the breadth of the issues relevant to health and the
environment, the report argues that the suggested programme should be
supported by several government departments. Interdepartmental support would
also be consistent with the desired inter-sector approach to the development and
implementation of policies on health and the environment.

The report concludes that the existing structures are adequate for the
purposes of knowledge synthesis.

Over the centuries, the adverse effects of our physical surroundings on public
health have been reduced by environmental management. Nevertheless, much
remains still to be done to protect public health against environmental hazards as
new factors continue to emerge and old factors threaten to reassert themselves.
The processes of globalisation are, at present, particularly important in this context. The Health Council therefore believes that there are compelling reasons for energetically implementing the measures announced in the fourth National Environmental Policy Plan, the *Action Plan Environmental Health* and the recently published European Strategy for the Environment and Health. The subjects identified in the report support that implementation.
Tetrachloroethylene (PER)


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 air at the workplace. These recommendations are made by the Councilís Dutch Expert Committee on Occupational Standards (DECOS). It constitutes the first step in a three-step procedure that leads to legally-binding exposure limits (MAC-values).

The present report is a co-production of DECOS and the Nordic Expert Group. In the report the committees discuss the consequences of occupational exposure to tetrachloroethylene (PER). Furthermore, DECOS recommends a health-based occupational exposure limit. The committeesí conclusions are based on scientific publications obtained from data retrieval systems prior to July 2002.

Physical and chemical properties

At ambient temperatures, PER is a colourless liquid with an ethereal odour. The compound is readily soluble in ethanol and diethylether; in water it can be dissolved up to a concentration of 150 mg/l. At 100 kPa its boiling point is 121°C and its freezing point -22.4°C.
PER is used as a solvent in dry cleaning, extraction and vapour degreasing of metals, as an intermediate in chemical synthesis, as an anthelminthic, as a heat-change fluid, and as a grain-fumigation agent.

**Monitoring**

Various validated methods exist for the determination of PER in ambient air and biological samples. In case of ambient air, active coal or Tenax* are used for adsorption. PER can be collected from biological samples by extraction, or by warming the sample, followed by trapping of the evaporated PER with an adsorbens. The adsorbed or extracted material is analyzed by means of gas chromatography with electron-capture detection, flame-ionization detection, or mass spectrometry.

Validated biological-monitoring methods are available. They are based on the analysis of exhaled air or blood for PER, and give a reliable impression of the (time weighted) average exposure over several days. Urinary excretion of trichloroacetic acid, which is the most important metabolite of PER in quantitative terms, is also proposed as a measure for human exposure. However, the analysis of the parent compound in exhaled air or blood is regarded to yield more reliable exposure estimates.

**Current limit values**

An occupational exposure limit (OEL; 8-h TWA) of 240 mg/m³ (35 ppm) is presently effective in the Netherlands. Sweden has a lower OEL, i.e. 69 mg/m³ (10 ppm). The United Kingdom established an OEL of 345 mg/m³ (50 ppm), 8-h TWA, while in the USA the American Conference of Governmental Industrial Hygienists (ACGIH) recommended an OEL of 170 mg/m³ (25 ppm), 8-h TWA.

Short-term exposure limits are established in Sweden (170 mg/m³, 25 ppm, 15-min TWA), the United Kingdom (689 mg/m³, 100 ppm, 15-min TWA), and by the ACGIH (685 mg/m³, 100 ppm, 15-min TWA).

Biological limit values are established in Germany (1 mg/l PER in blood prior to next shift) and by the ACGIH (5 ppm PER in expired air and 0.5 mg/l PER in blood prior to last shift of workweek, and 3.5 mg/l trichloroacetic acid in urine at the end of the workweek). The compound received a skin notation in the Netherlands.

* A polymeric material used for the sorption of gaseous organic compounds from air. Desorption can be achieved by heating; i.e., without the need of dissolving the sorbed compounds in a solvent.
Kinetics

Actually all inhaled PER enters the blood. Depending on concentration inhaled, absorption percentages of 50-90% have been observed in humans under steady-state conditions.

Data on dermal absorption are scanty. However, immersion of the thumb in PER has been found to correspond with a respiratory exposure to 1.4 - 4.1 mg/m³ (0.2-0.6 ppm). For mice an absorption rate of 24.4 nmol/min per cm² has been determined. Dermal absorption of PER vapour is negligible compared to the respiratory absorption of the same vapour. Based on animal experiments, the oral absorption can expected to be actually complete.

PER accumulates in the fat tissues. It is unknown how long it takes before an equilibrium is reached between accumulation in the fat and elimination from the fat. Furthermore, relatively high concentrations of PER are to be expected in brain, kidneys, liver and lungs.

In humans, the major part of the absorbed PER is eliminated in unaltered form via exhalation, while only a small fraction is metabolized (estimated to be 1-2%). The major metabolite is trichloroacetic acid, a product of an oxidative biotransformation pathway, which is excreted in the urine. Very low concentrations of a product of glutathione conjugation have been detected in human urine. The importance of this finding lies in the possible association with the formation of genotoxic metabolites in the kidney as a result of glutathione conjugation.

Half lives for respiratory elimination vary from 1-72 h for humans, depending on the relative concentrations of PER in blood, fat and other tissues.

Effects

Irritation and sensitisation

PER is a skin- and eye-irritating compound. Human volunteer studies showed that exposure to concentrations below 690 mg/m³ (100 ppm) resulted in transient irritation of the eyes, nose and throat. Although negative in an animal test for skin sensitisation, human case studies show that skin sensitisation may occasionally occur under occupational conditions. There are no clear indications for respiratory sensitisation.
Lethality

The compound has a low acute lethality after respiratory or oral exposure. Respiratory LC50 values have been found to vary between 3000 and 6000 ppm (20,700 and 41,340 mg/m³), depending on animal species and exposure time. Lethality is caused by respiratory failure, which, in its turn, is a result of acute neurotoxicity.

Neurotoxicity

Acute toxic respiratory exposure gives rise to a series of clear-cut neurotoxic effects in man and experimental animals. The compound causes a reversible depression of the central nervous system, which has lead in the past to its use as a human anaestheticum. High doses lead to coma, followed by respiratory failure and death.

Case reports suggest that longer-term respiratory exposure between 1378 mg/m³ (200 ppm) and 2756 mg/m³ (400 ppm) of PER results in various reversible neurological effects in humans. Also in a human volunteer study reversible neurological symptoms have been found at about 690 mg/m³ (100 ppm). The neurotoxicity of PER is confirmed by several epidemiological studies. Overall, the available information makes clear that neurotoxic effects have to be expected in humans after exposures to concentrations of about 690 mg/m³ (100 ppm) and higher. Reported effects include: headache, dizziness, lightheadedness, flushing, difficulty in speaking, sleepiness, loss of inhibitions, exhilaration, feelings of elation, and impaired motor coordination.

Some studies suggest neurological effects below 690 mg/m³ (100 ppm): volunteers exposed to 345 mg/m³ PER (50 ppm) showed increased visual evoked potentiali and visual contrast sensitivity thresholds, whereas in another study increased serum prolactine levels and poor neurological responses were observed at a concentration of as low as 100 mg/m³ (median level). However, due to methodological shortcomings, or inconclusive results, these studies were not used by DECOS for hazard-assessment purposes.

The neurotoxic effects observed in short-term inhalation studies with experimental animals, do not differ essentially from those observed in acute inhalation studies. Lower concentrations can to a certain extent be compensated for by longer exposure. However, adaptation develops upon repeated exposure.
Hepatotoxicity and nephrotoxicity

In experimental animals, acute respiratory toxicity comprises effects on the liver and the kidneys at doses approaching anaesthetic or lethal levels. Temporary liver and kidney damage has also been reported in cases of acute poisoning of humans by inhalation.

In case reports, effects on the liver were described after longer-term respiratory exposure between 1378 and 2756 mg/m³ (200 and 400 ppm). A single case report indicated that PER can be transferred to breast milk and might cause jaundice in breast-fed babies.

Short-term respiratory and oral exposure of experimental animals resulted in (histo)pathological and biochemical effects in the liver, among them peroxisome proliferation. As the severity of these effects was correlated with the rate of oxidative PER biotransformation, they were most probably caused by products of this metabolic pathway. Trichloroacetic acid has been identified as an important hepatotoxic metabolite. This compound is an effective inducer of peroxisome proliferation, and is, therefore, held responsible for this effect in experimental animals after PER exposure.

Nephrotoxicity has also been observed in respiratory and oral short-term studies. For mice, a no-observed-adverse-effect-level (NOAEL) of 690 mg/m³ (100 ppm) is established, based on tubular karyomegaly. Peroxisome proliferation has been observed in mouse kidneys, but not in rat kidneys, upon oral exposure by gavage to 1 g/kg bw/day for 10 days. In another study, exposure by gavage of rats for 28 days to 500 mg/kg bw/day resulted in histopathological and biochemical effects pointing to tubular damage. Protein-droplet accumulation was found specifically in male rats after 10 daily gavage doses of 1 g/kg.

The chronic studies confirmed the hepato- and nephrotoxicity of PER. The latter effect showed a clear-cut sex dependence in rats, males being much more sensitive than females.

Haematological effects

Exposure by inhalation of mice to 930 mg/m³ (135 ppm) and 1860 mg/m³ (270 ppm) (6 h/day, 5 days/week, 7.5 weeks) resulted in reversible effects on white-blood-cell counts.
Carcinogenicity

Several epidemiological studies dealt with the effects of PER exposure on cancer incidence or cancer mortality. No effects were found on the endpoints indicated by animal studies (carcinoma in liver and kidneys and leukemia). Interpretation of many epidemiological studies is hampered by concomitant exposure to other solvents in industry and limited treatment of risks of lifestyle-related factors. Some studies point to an increased risk of oesophagus cancer, which cannot (fully) be attributed to lifestyle-related factors as smoking and drinking.

Statistically significant increases of the incidence of hepatocellular carcinoma were found in mice upon respiratory and oral exposure. These tumours are also induced in mice when they are treated orally with trichloroacetic acid, the major oxidative metabolite of PER, which indicates the carcinogenic effect to be the result of the formation of this compound. As both PER and its major metabolite induce peroxisome proliferation, it is generally assumed that the liver carcinogenicity depends on this effect.

In male rats, a small and statistically insignificant increase of renal tubular-cell adenoma and carcinoma was found in a chronic inhalation study. In so far as this finding can really be attributed to the treatment, it is probably connected to protein-droplet formation. However, the results of the study in question do not allow for a definitive conclusion on this point. The study also revealed a statistically significant increase of the incidence of mononuclear cell leukemia. However, the background incidence of this effect in the rat strain used appeared to be very high.

Genotoxicity

PER was extensively tested for genotoxicity with many combinations of endpoint and test organism. On the whole, the results warrant the conclusion that exposure to PER does not present a genotoxic risk to humans.

Reproduction toxicity

There is some epidemiological evidence for adverse effects on fertility (sperm quality) and on developmental toxicity (increased risk of spontaneous abortion) in dry cleaners. However, a possible contribution of PER could not be distinguished from contribution of other solvents used in dry cleaning.
No clear signs for teratogenicity were found in animal studies at high doses, however, some indication of fetotoxicity was observed. In a multigeneration reproduction study, some decreases in litter size and survival during lactation were seen at 6900 mg/m\(^3\) (1000 ppm) but not at 2070 mg/m\(^3\) (300 ppm). At 6900 mg/m\(^3\) also some maternal toxicity was observed.

Hazard assessment, HBR-OEL and skin notation

PER has skin- and eye-irritating properties, and has incidentally been shown to induce skin sensitisation in man. The effects observed at the lowest concentrations are largely neurological in origin. Taken together, the available human database shows that affected neurological functions start to become manifest at doses around 690 mg/m\(^3\) (100 ppm).

In a few long-term human exposure studies, hepatotoxicity was observed between 1378 and 2756 mg/m\(^3\) (200 and 400 ppm). It is not justifiable to use hepatotoxicity data in experimental animals as a starting point in quantitative hazard assessment. Experimental animals (especially mice) have a specifically high sensitivity to the hepatotoxic effects of PER which is most probably linked with its high rate of oxidative biotransformation of PER. The hepatotoxic effects are, therefore, regarded by the committees to be irrelevant to humans in terms of predicting health effects in humans caused by exposure to PER.

Adequate human data on nephrotoxicity are lacking. Due to the differences in biotransformation in case of nephrotoxicity, the results of experimental animals studies are inadequate for extrapolation to humans as well.

The committees regard neurotoxicity as the most sensitive effect of human exposure to PER. The adverse effects on neurological functions are observed at a concentration of as low as 690 mg/m\(^3\). Some studies suggest that exposure to PER below 690 mg/m\(^3\) may lead to adverse neurological effects. However, both committees regard these studies as inconclusive, because of methodological shortcomings.

For deriving a health based occupational exposure limit (HBR-OEL), DECOS considers the concentration of 690 mg/m\(^3\) as the lowest-observed adverse effect level (LOAEL). At this concentration also eye-irritation is observed. A relatively large safety factor of five is applied for extrapolation from the LOAEL to the NAEL, taken into account the existence of inconclusive evidence for some minor neurological effects at concentrations lower than 690 mg/m\(^3\). Applying this safety factor, DECOS recommends a HBR-OEL for PER of 138 mg/m\(^3\) (20 ppm), as an eight-hour time-weighted average concentration.
As dermal exposure can substantially contribute to the body burden with PER, the DECOS recommends a skin notation.

**Health-based recommended occupational exposure limit**

The Dutch Expert Committee on Occupational Standards recommends a health-based Occupational Exposure Limit for PER of 138 mg/m³ (20 ppm), 8-h TWA, as well as a skin notation.
Formaldehyde

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 air at the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS). They constitute the first step in a three-step procedure that leads to legally binding limit values.

The present report is a co-production of DECOS and the Nordic Expert Group. In the report the committees discuss the consequences of occupational exposure to formaldehyde. In conformity with its mission, DECOS had evaluated the data in order to derive a health-based occupational exposure limit. This assessment is an update of previous documents published by DECOS in 1981 (RA 4/81) and 1987 (RA 3/87).

The committees' conclusions are based on scientific publications prior to October 2002.

Physical and chemical properties
Formaldehyde is a colourless gas at normal temperature and pressure. It is flammable, reactive and readily polymerizes at room temperature. It forms explosive mixtures with air and oxygen at atmospheric pressure. Formaldehyde is present in aqueous solutions as a hydrate and tends to polymerize. Under
atmospheric conditions, formaldehyde is readily photo-oxidized in sunlight to carbon dioxide.

The relative molecular mass of formaldehyde is 30.03, the boiling point is -200°C and the melting point -92°C. The compound is miscible in water.

Formaldehyde is used as a raw material in chemical reactions, is an intermediate in the manufacture of numerous products and has a wide medical application as a disinfectant or as a preservative.

**Monitoring**

The most widely used methods for the determination of formaldehyde concentrations are based on photometric measurements. The type of sampling depends on the medium in which formaldehyde is to be determined. Formaldehyde in air may be collected in an absorbing medium by diffusion (passive sampling). For active sampling, aqueous solutions and solutions containing sulfite, 3-methyl-2-benzothiazolene hydrazine (MBTH), chromotropic acid or 2,4-dinitrophenylhydrazine (DNPH) are generally used for absorption.

Biological monitoring methods for exposure to formaldehyde have not been assessed in any detail. Given the knowledge of its critical effects and the target organs, the committees see no need for biological monitoring.

**Current limit values**

The current occupational exposure limit for formaldehyde in the Netherlands is 1.5 mg/m³ (1 ppm), TWA-8 h and 3.0 mg/m³ (1.5 ppm), TWA-15 min. This limit is still not legally binding.

The American Conference of Governmental Industrial Hygienists (ACGIH) has set a Threshold Limit Value of 0.37 mg/m³ (0.3 ppm), as a ceiling and classified formaldehyde as a suspected human carcinogen, Group A2. The Deutsche Forschungsgemeinschaft endorsed a MAK value of 0.37 mg/m³ (0.3 ppm) as an 8 hour time-weighted-average (TWA-8 h), with a notation as a sensitizing agent, and classified formaldehyde into carcinogen category 4 (genotoxicity playing no or at most a minor part).

The United Kingdom adheres to an MEL of 2.5 mg/m³ (2 ppm), TWA-8 h.

The European Union has classified the carcinogenic effects of formaldehyde in category 3.
Toxicokinetics

Under normal conditions, inhaled formaldehyde is absorbed in the upper respiratory tract. After absorption of 14C-formaldehyde, radio-activity is distributed to various organs and tissues with the highest concentrations found in the oesophagus, followed by the kidneys, liver, intestine and lungs. Retention in the nasal passages of the rat was estimated at 93% of the inhaled amount, regardless of airborne concentrations. It was estimated that absorption of concentrated solutions of formalin through the skin amounted to 319 mg/cm² per hour.

Formaldehyde is a normal metabolite in mammalian systems and it is rapidly metabolized to formate, which is partially incorporated via normal metabolic pathways into the one-carbon pool of the body or further oxidized to carbon dioxide. There are two pathways of final elimination: via exhalation and via the kidneys.

Effects

The target organs of formaldehyde vapour are the eyes, nose and throat.

The predominant effect of short-term formaldehyde exposure in humans is sensory irritation, first experienced in the eyes, followed by perception of the odour and then irritation of the nose and throat accompanied by discomfort, lachrymation, sneezing, coughing, nausea and dyspnoea. For most individuals sensory irritation does only slightly occur until an (short-term) exposure concentration of 1.2 mg/m³ (1 ppm).

However, at lower exposure levels (0.26-0.29 mg/m³ (0.22-0.24 ppm) for a longer time period sensory irritation may still occur in a substantial percentage of exposed persons. In one, not well documented, study, 19% of the exposed subjects still reported eye irritation at an exposure concentration of 0.29 mg/m³ (0.24 ppm). No changes in pulmonary function have been found in humans exposed to formaldehyde concentrations up to 3.6 mg/m³ (3 ppm).

In experimental animals, irritation of eyes, nose, throat and lungs was observed at exposure concentrations higher than 2.4 mg/m³ (2.0 ppm). In mice a 10-min RD50 (the concentration associated with a 50% decrease in respiratory rate) for formaldehyde of 3.6 ± 0.34 mg/m³ (3.0 ppm ± 0.28 ppm) has been reported.

There is no convincing evidence of formaldehyde being able to sensitize the respiratory tract. Skin sensitization is induced by direct skin contact with
formaldehyde solutions in concentrations higher than 2%. Formaldehyde-induced allergic contact dermatitis has been estimated to occur in 3 to 6% of the population. There is overwhelming evidence that high concentrations of formaldehyde vapour (12 mg/m³ (10 ppm) or higher) can induce nasal cancer in rats but there is no convincing evidence for respiratory tract cancer risk in humans.

Three different meta-analyses of epidemiological studies have shown inconsistent results. In two of them, a relationship between exposure to formaldehyde and the occurrence of nasopharyngeal cancer was observed, while an association with nasal cancer was ambiguous. In these two meta-analyses, the authors did not correct for the unreported studies in which no cases of nasal cancers were found. This must have led to an overestimation of the overall relative risk for nasopharyngeal cancer. In a third, more recently published meta-analysis, this correction for the underreporting was made. In addition, the exposure potential for the jobs included in the analysis was evaluated. The authors concluded that the epidemiological studies do not support a causal relationship between formaldehyde exposure and nasopharyngeal cancer. The committees endorse this conclusion and further conclude that the currently available epidemiological database does not provide support for a nasal cancer risk at exposure levels lower than 0.3 mg/m³ (LOAEL for sensory irritation). Also from the epidemiological studies it seems unlikely that exposure to formaldehyde affects lung cancer risk.

The effects of short-term exposure to airborne formaldehyde in experimental animals are cytotoxic damage to and regenerative proliferation of the nasal respiratory epithelium. The histopathological changes range from slight hyperplasia and squamous-cell metaplasia of the ciliated and non-ciliated respiratory epithelium in specific areas (found at low effective exposure concentrations, i.e. 2.4 to 3.6 mg/m³ (2 to 3 ppm)) to severe rhinitis, necrosis and extensive hyperplasia and metaplasia of major portions of the nasal respiratory epithelium (found at exposure concentrations of about 7.2 mg/m³ (6 ppm) and higher. Substantial increases in nasal epithelial cell turnover rates occur in rats after exposure to concentrations of 7.2 mg/m³ (6 ppm). Most NOAELs in these short-term studies were found between 1.2 and 2.4 mg/m³ (1 or 2 ppm). In all studies with a NOAEL of 1.2 mg/m³ (1 ppm) the LOAEL was higher than 2.4 mg/m³ (2 ppm). This might indicate that also in these studies 2.4 mg/m³ might have been a NOAEL if indeed this exposure level would have been included in these experiments. However, (slightly and transiently) increased cell turnover
rates have occasionally been found at levels between 0.6 to 2.4 mg/m^3 (0.5 to 2 ppm).

Effects after long-term inhalation exposure to formaldehyde in experimental animals include inflammatory, degenerative and regenerative changes of the nasal mucosa and squamous-cell carcinomas of the nasal respiratory epithelium. The non-neoplastic nasal changes range from a minimal degree of hyperplasia and squamous-cell metaplasia of the nasal respiratory epithelium (occasionally seen at concentrations of approximately 2.4 mg/m^3 (2 ppm) or lower) to rhinitis, necrosis and extensive restorative hyperplasia and metaplasia of the nasal respiratory epithelium invariably seen at concentrations of about 7.2 mg/m^3 (6 ppm) and higher. High incidences of squamous-cell carcinomas have been found in rats at exposure levels of 12 mg/m^3 (10 ppm) or higher. In most long-term studies, a NOAEL of 1.2 or 2.4 mg/m^3 has been reported. However, in one long-term study in rats 2.4 mg/m^3 (2 ppm) appeared to be a LOAEL and in another long-term rat study a LOAEL as low as 0.36 mg/m^3 (0.3 ppm) was reported.

No adequate data were available on genetic effects of formaldehyde in humans. Formaldehyde is comprehensively genotoxic in a variety of experimental systems, ranging from bacteria to rodents in vivo. Formaldehyde given by inhalation or gavage to rats induced chromosomal aberrations in lung cells, micronuclei in gastro-intestinal tract cells and sperm-head anomalies. Inhalation of formaldehyde leads to formation of DNA-protein cross-links in the nasal respiratory epithelium of rats and monkeys. The formation of DNA-protein cross-links is a sublinear function of the formaldehyde concentration in inhaled air from 0.86 to 18.4 mg/m^3 (0.7-15 ppm). There is no detectable accumulation of DNA-protein cross-links during repeated exposures. In V79 Chinese hamster cells, formaldehyde induced DNA-protein crosslinks, sister-chromatid exchanges and micronuclei, but no gene mutations, in concentrations similar to those inducing cytotoxicity, suggesting that formaldehyde-induced DNA-protein crosslinks are related to cytotoxicity and clastogenicity. It has been suggested that the nasal inflammation and proliferation induced by formaldehyde exposure may contribute to the induction of genetic alterations through a variety of mechanisms including generation of reactive oxygen species, alterations in nucleotide pools, free radical formation, and clonal expansion with further mutation of genetically altered cells.

With respect to the mechanism underlying the nasal carcinogenicity of formaldehyde in rats, there is a large body of data suggesting an association between the cytotoxic, genotoxic and carcinogenic effects of formaldehyde. The steep non-linear dose-response curve for nasal tumours ó indicating a more than
proportionate decrease in carcinoma incidence at low concentrations ó is most probably due to the fact that defence mechanisms of the nose (mucociliary clearance, detoxification by dehydrogenase, DNA repair) are very effective at low concentrations, but can be overwhelmed and inactivated at high concentrations; consequently, cell and tissue damage and finally tumours occur at high concentrations only. This also means that formaldehyde in concentrations not leading to tissue damage most probably cannot act as a complete carcinogen (causing initiation, promotion and progression).

In several animal studies, inhalation of formaldehyde was not found to affect reproduction.

Hazard assessment*

From the toxicological data base, it was evident that the effects of concern of formaldehyde are sensory irritation and cytotoxicity-induced regenerative hyperplasia and metaplasia of the nasal respiratory epithelium accompanied by nasal carcinomas in rats after long-term exposure to high cytotoxic concentrations.

Controlled studies in volunteers revealed a wide variation in individual susceptibility to sensory irritation from formaldehyde. For most persons sensory irritation (eye, nose and/or throat) did not occur until an exposure concentration of at least 1.2 mg/m³ (1.0 ppm). However, at lower exposure levels sensory irritation may still occur in a substantial percentage of exposed individuals, and in one, not well documented study 19% of the exposed subjects reported eye irritation at an exposure concentration of 0.29 mg/m³ (0.24 ppm). In experimental animals, irritation of eyes, nose, throat and lungs was observed at exposure concentrations greater than 2.4 mg/m³ (2.0 ppm).

Overall, weighing the total body of data, both committees estimated that 0.3 mg/m³ (0.25 ppm) formaldehyde is the lowest observed adverse effect level (LOAEL) at which sensory irritation may occur in a low but significant percentage of exposed workers. Therefore, based on sensory irritation only, DECOS would recommend a HBR-OEL for formaldehyde of 0.15 mg/m³ (0.12 ppm), providing a margin of safety (of 2) which DECOS considers large enough to prevent significant sensory irritation in workers, taking into account that (I) the critical effect (sensory irritation) is a local effect, (II) the incidence of the effect at 0.3 mg/m³ is low (19%) and may not be different from the background.

* For the recommendation of a health-based occupational exposure limit only DECOS takes responsibility.
incidence in controls and (III) minimal sensory irritation may rapidly subside due to accommodation.

Then, the DECOS discussed whether an exposure limit of 0.15 mg/m³ (0.12 ppm), is low enough to protect workers against cytotoxic-induced hyperproliferation of the nasal respiratory epithelium, and consequently also against the potential risk of nasal cancer.

Nasal carcinomas in rats have only been found after exposure to high, cytotoxic concentrations causing rhinitis, necrosis and regenerative hyperplasia and squamous metaplasia of the nasal respiratory epithelium. The crucial role of tissue damage followed by hyperplasia and metaplasia of the nasal respiratory epithelium in formaldehyde carcinogenesis has been demonstrated in a convincing way, has meanwhile been widely recognized, and has been included in human cancer risk assessment of formaldehyde. The committees found it reasonable to conclude that the response of the respiratory tract to formaldehyde will be qualitatively similar in rats and humans. If in humans exposure of formaldehyde is accompanied by recurrent tissue damage at the site of contact, formaldehyde may be assumed to have carcinogenic potential in man via mechanisms of cytotoxicity. Correspondingly, if the respiratory tract tissue is not recurrently injured, exposure of humans to relatively low, non-cytotoxic levels of formaldehyde can be assumed to be associated with a negligible cancer risk.

Both committees (DECOS and NEG) observed that the majority of short- and long-term inhalation studies with formaldehyde in experimental animals reveals a NOAEL of 1.2 or 2.4 mg/m³ (1 or 2 ppm). However, in a few studies slight histopathological changes of the nasal respiratory epithelium were observed at levels ranging from 0.36 to 2.4 mg/m³ (0.3 to 2 ppm) formaldehyde.

Three meta-analyses of human epidemiological studies have shown inconsistent results. In two of them a significant relation between exposure to formaldehyde and nasopharyngeal cancer risk was observed. The association between formaldehyde exposure and nasal cancer was ambiguous. However, according to the committees, in these meta-analyses the authors did not correct for the unreported studies in which no cases of nasal cancers were found. This must have led to an overestimation of the overall relative risk of nasopharyngeal cancer. In the third, more recent, published meta-analysis, a correction was made for underreporting, and the authors concluded that there was no support for a causal relation between formaldehyde exposure and nasopharyngeal cancer. The committees endorsed this conclusion and concluded that the currently available epidemiological database on formaldehyde does not provide evidence for a
Research indicates a respiratory tract cancer risk at exposure levels lower than 0.3 mg/m³ (LOAEL for sensory irritation).

In conclusion, DECOS is of the opinion that an health based occupational exposure limit (HBR-OEL) of 0.15 mg/m³ (0.12 ppm) formaldehyde is low enough to protect workers against nasal tissue damage, and as a consequence, also against the potential risk of nasal cancer.

To avoid peak exposures possibly entailing cytotoxicity-induced hyperproliferation and metaplasia of the nasal respiratory epithelium, the DECOS recommends a Short Term Exposure Limit (STEL). Data from human studies indicate that short term exposure to formaldehyde at concentrations up to approximately 1.0-1.2 mg/m³ leads to slight irritation of the eyes only. Therefore, the DECOS recommends a STEL of 0.5 mg/m³ (twa 15 minutes) which is considered low enough to avoid any significant sensory irritation, and thus nasal toxicity as well.

**Recommended occupational exposure limit**

DECOS recommends a health-based occupational exposure limit of 0.15 mg/m³ (0.12 ppm) formaldehyde in air, TWA-8 h, and a short term exposure limit, 15 min TWA, of 0.5 mg/m³ (0.42 ppm).
Sulphur dioxide


Scope

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands sets Health-Based Recommended Occupational Exposure Limits (HBR-OEL) for chemical substances in air in the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS). They constitute the first step in a three-step procedure, which leads to legally binding occupational exposure limits.

In this report, the committee discusses the consequences of occupational exposure to sulphur dioxide and recommends a health-based occupational exposure limit. The committee's conclusions are made on the documents produced by the Scientific Committee on Occupational Exposure Limits of the European Commission (SCOEL; SCO93, SCO98) and on additional scientific papers published prior to May 2002.

Physical and chemical properties

Sulphur dioxide (SO₂; CAS no. 7446-09-5) is a colourless gas, with an irritating odour. Its odour threshold ranges between 0.8 and 8 mg/m³. The molar mass of sulphur dioxide is 64.06 g/mol, its melting point -72.7°C and its boiling point -10.0°C. Sulphur dioxide is highly hydrophilic and dissolves easily in water.
Sulphur dioxide is used in the inorganic and petrochemical industries, such as in the production of cellulose pulp and chemicals. The substance has a lot of functions: as an antioxidant in the bromine production; as a bleaching gas in casting magnesium parts and bleaching kaolin; as a rapid catalyst in furfural resins for manufacturing casting moulds; as a fruit and vegetable preservative in the food; and, as a disinfectant in the wine and brewery industry.

**Monitoring**

Various sampling and analysis techniques are available for determining ambient concentrations of sulphur dioxide in an occupational setting. Both passive and active samplers may be used. Samples obtained from passive sampling are analysed by spectrophotometry or ion exchange chromatography. The National Institute for Occupational Safety and Health (NIOSH) recommends the latter (Method 6004; detection range: 0.5-20.0 mg/m\(^3\) per 100 L air sample).

Concerning personal exposure, direct reading pocket dosimeters may be used, as is described in a protocol, called ‘Voornorm NVN 2950’, from the Dutch Normalisation Institute.

**Limit values**

In 1985, the DECOS recommended an HBR-OEL for sulphur dioxide of 1.3 mg/m\(^3\), as an 8-hour time weighted average (8-hour TWA). However, due to socio-economic constraints, the Netherlands has set a legal occupational exposure limit (OEL) of 5 mg/m\(^3\) (8-hour TWA). In addition, the SCOEL has set a limit of 1.3 mg/m\(^3\) (8-hour TWA) and of 2.7 mg/m\(^3\) (15-minute TWA). Both in Germany and Denmark, OELs have been set at 1.3 mg/m\(^3\), averaged over an 8-hour period of time; and, in the United Kingdom and Sweden of around 5 mg/m\(^3\) (8-hour TWA) and 13 mg/m\(^3\) (15-minute TWA, for Sweden a Ceiling). Finally, the American Conference of Governmental Industrial Hygienists has proposed a TLV of 5 mg/m\(^3\) and a STEL of 13 mg/m\(^3\).

**Kinetics**

Inhaled sulphur dioxide is mainly absorbed in the body through the epithelium of the upper respiratory tract (nose and throat). However, the substance may reach the lower respiratory tract (bronchi and alveoli in lungs) when it is deeply inhaled, as happens with doing heavy work or physical exercise.
Sulphur dioxide is a highly hydrophilic gas. Therefore, it reacts easily with water, which is present at the surface of the respiratory tract. When sulphur dioxide reacts with water sulphurous acid is formed. This sulphurous acid dissociates easily into sulphite and bisulphite ions. Sulphite ions are then rapidly converted into sulphate, whereas bisulphite ions bind to proteins to form S-sulphonates. In the blood most of the sulphur dioxide is present as S-sulphonate and only a minor part as free sulphite/sulphate or bisulphite ions. Sulphates are quickly absorbed in the large endogenous sulphate pool of the body and then slowly released via the blood into the urine. Circulating S-sulphonates slowly decompose into sulphates or sulphur dioxides. The latter substance is exhaled.

**Effects**

In humans, sulphur dioxide is irritating to the eyes and the upper respiratory tract. Inhaling high concentrations may cause: rhinorrhea; coughing; shortness of breath; chest tightness; and, a choking sensation.

Epidemiological studies have associated chronic sulphur dioxide exposure with chronic coughing; bronchitis; increased susceptibility to airway infections; and, increased susceptibility to allergy by airborne allergens. However, because these studies included several confounding factors, they are considered insufficient for quantitative risk assessment.

A number of laboratory studies have been carried out with healthy, non-smoking volunteers, who were exclusively exposed to sulphur dioxide. These volunteers were exposed to concentrations of as low as 0.53 mg/m³ to more than 60 mg/m³. The exposures lasted from minutes up to several hours and were carried out with or without physical exercise. The main adverse effects observed were irritation of the upper respiratory tract and the eyes, and decreased lung function, such as increased pulmonary airway resistance. These adverse effects were clearly present at exposure levels of 2.7 mg/m³ or higher. None of these effects were observed at exposure levels below 2.0 mg/m³, with the exception of three studies (two of the same research group): these three studies were, however, not considered for risk assessment, because of limitations in study design or the lack of toxicological relevance of the findings. In addition, at 2.0 mg/m³, two independent studies were performed with volunteers, who were exposed for 40 minutes and 4 hours, respectively, with moderate physical exercise. In all these volunteers lung function remained normal. Based on these outcomes, the committee considers 2.0 mg/m³ as the No Observed Adverse Effect Level (NOAEL) after short-term exposure.
Epidemiological data obtained from the general population indicate that people with asthma or with other diseases concerning the respiratory tract are more vulnerable to sulphur dioxide exposure than healthy people. Concerning asthma, this finding is supported by laboratory data. However, numerous studies with asthmatics show that the level of susceptibility is strongly influenced by non-specific factors, such as physical activity and atmospheric conditions (dry, cold air). These factors alone may aggravate asthma. Therefore, the committee cannot conclude whether or not asthmatics are more vulnerable to sulphur dioxide exposure in the absence of these non-specific stimuli. However, it is concerned that asthmatics are at higher risk when exposed to sulphur dioxide in combination with these non-specific asthma-aggravating factors.

Data from experiments in animals with acute or short-term exposure support the findings in humans, that sulphur dioxide irritates the (upper) respiratory tract and eyes and reduces respiratory defence mechanisms against bacterial infections. In addition, changes in enzyme activities in liver and blood were observed. However, the committee noted that the quality of the reporting of most of these studies was insufficient. Apart from that, most animals were exposed to very high levels (up to 267 mg/m³ (subchronic) or >1,000 mg/m³ (acute)).

The exposure levels in long-term animal studies were lower than in short-term animal studies (0.35 up to 133 mg/m³). However, no concentration-response relationships could be established, because data were too limited to be useful for quantitative risk assessment.

Few animal studies have been directed towards the carcinogenicity of sulphur dioxide. Although tumour formation was observed, the studies showed considerable limitations, including: the use of animals with very high spontaneous tumour incidence; exposure to high levels of the substance; and, incomplete reporting on the tumour promoting activity of sulphur dioxide in combination with benzo[a]pyrene.

In regard to genotoxicity, mutagenicity tests in bacteria scored positive in conditions not relevant for humans. Also, sulphur dioxide induced chromosomal aberrations \textit{in vitro}, and micronuclei \textit{in vitro} and \textit{in vivo}.

In a limited number of experiments, the adverse effects of sulphur dioxide have been studied on reproduction. Litter of rabbits and mice were exposed to 187 and 67 mg/m³, respectively. This resulted in minor skeletal variations and mild maternal toxicity. In another study, offspring of exposed mice (13.4 to 80 mg/m³)
showed no defects in reproductive performance, and in somatic and neurobehavioral development.

**Evaluation**

From the current data, the committee concludes that the acute effects of sulphur dioxide on the respiratory tract, such as nose and throat irritation, depressed lung function and increased airway resistance, should be prevented. In order to do this, the committee recommends deriving a health-based occupational exposure limit for short-term exposure (Short-Term Exposure Limit (STEL); 15-min TWA).

From the human database a NOAEL of 2.0 mg/m³ was derived (see previous paragraph). In addition, to the committee’s opinion the NOAEL needs to be adjusted for inter-individual differences. This is needed, because the number of studies at the NOAEL and the number of participants in those studies were limited. Also, the committee is aware of the reporting of variable responses among healthy people at levels near the NOAEL. To compensate for these uncertainties, a factor of 3 was chosen. Consequently, the committee recommends a STEL for sulphur dioxide of 0.7 mg/m³ (=0.25 ppm).

Both epidemiological and animal data suggest that chronic exposure to sulphur dioxide may lead to chronic irritation (bronchitis) and increased susceptibility to airway infections. However, these data were not reliable or insufficient to assess concentration-response relationships. For this reason, the committee does not recommend an HBR-OEL (8-h TWA).

Concerning workers with a possible extra risk, the committee likes to express its concern that asthmatics are at a higher risk when not only exposed to sulphur dioxide, but also to other (non-specific) factors which incite asthma.

Carcinogenicity and genotoxicity data are too limited to make a definite conclusion about the carcinogenic potential of sulphur dioxide in humans. Therefore, the committee recommends not classifying sulphur dioxide as a suspected carcinogen. In addition, the database is too restricted to allow any conclusion to be drawn on the adverse effects on fertility and development.
Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Standards recommends a health-based occupational exposure limit for sulphur dioxide of 0.7 mg/m³ (≈0.25 ppm), as a 15-minute time weighted average concentration (STEL).
Strong inorganic acid mists containing sulphuric acid


At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates the carcinogenic properties of substances at the workplace and proposes a classification with reference to the EU-directive. The Dutch Expert Committee on Occupational Standards performs this evaluation. The present report contains an evaluation by the committee on the carcinogenicity of strong inorganic acid mists containing sulphuric acid.

The committee concludes that strong inorganic acid mists containing sulphuric acid are known to be carcinogenic to humans (comparable with EU category 1). These inorganic acid mists act by a non-stochastic genotoxic mechanism*.

* This means that an occupational exposure limit can be derived using a threshold model. Such an exposure limit cannot be derived for genotoxic carcinogens. In the latter case, the committee estimates additional lifetime cancer risks using a linear extrapolation model as a default method.
Metallic lead

On request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates the effects on the reproduction of substances at the workplace. The Health Council's Committee for Compounds Toxic to Reproduction recommends to classify compounds toxic to reproduction according to the Directive 93/21/EEC of the European Union. In the present report the committee has reviewed metallic lead.

The committee is of the opinion that metallic lead should be classified consistent with inorganic lead compounds (which have already been classified by the European Union).

The committee's recommendations are

• For effects on fertility, the committee recommends to classify metallic lead in category 3 (substances which cause concern for human fertility) and to label with R62 (possible risk of impaired fertility).
• For developmental toxicity, the committee recommends to classify metallic lead in category 1 (substances known to cause developmental toxicity in humans) and to label with R61 (may cause harm to the unborn child)
• For effects during lactation, the committee recommends that metallic lead should be labelled with R64 (may cause harm to breastfed babies).
Tetrachloroethylene (PER)

On request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates the effects on the reproduction of substances at the workplace. The Health Council’s Committee for Compounds Toxic to Reproduction recommends to classify compounds toxic to reproduction according to the Directive 93/21/EEC of the European Union. In the present report the committee has reviewed tetrachloroethylene. The committee’s recommendations are

- For effects on fertility, the committee recommends not to classify tetrachloroethylene on the basis of a lack of sufficient human data and sufficient animal data which show that no classification is indicated.
- For developmental toxicity, the committee recommends to classify tetrachloroethylene in category 3 (substances which cause concern for humans owing to possible developmental effects) and to label tetrachloroethylene with R63 (possible risk of harm to the unborn child).
- For effects during lactation, the committee is of the opinion that due to a lack of appropriate data tetrachloroethylene should not be labelled.
Nickel and its compounds

On request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates the effects on the reproduction of substances at the workplace. The Health Council's Committee for Compounds Toxic to Reproduction recommends to classify compounds toxic to reproduction according to the Directive 93/21/EEC of the European Union. In the present report the committee has reviewed nickel and its compounds.

The committee's recommendations are:

• Metallic nickel
  • for effects on fertility, the committee recommends no classification of metallic nickel, due to a lack of appropriate data
  • for developmental toxicity, the committee recommends not to classify metallic nickel due to a lack of appropriate data
  • the committee is of the opinion that a lack of appropriate data precludes the labelling of metallic nickel for effects during lactation.
• Nickel carbonyl
  • for effects on fertility, the committee recommends no classification of nickel carbonyl, due to a lack of appropriate data
  • For effects on development, the committee recommends to classify nickel carbonyl in category 3 (substances which cause concern for humans owing to possible developmental effects) and to label the compound with R63 (possible risk of harm to the unborn child).
• the committee is of the opinion that a lack of appropriate data precludes the labelling of nickelcarbonyl for effects during lactation.

• Soluble nickel salts
  • For effects on fertility, the committee recommends to classify the soluble nickel salts in category 3 (*substances which cause concern for human fertility*) and to label the compounds with R62 (*possible risk of impaired fertility*)
  • For effects on development the committee recommends to classify the soluble nickel salts in category 2 (*substances which should be regarded as if they impair fertility in humans*) and to label the compounds with R61 (*May cause harm to the unborn child*).
  • for effects during lactation, the committee recommends that the soluble nickel salts should be labelled with R64 (*may cause harm to breastfed babies*).

• Insoluble nickel salts
  • for effects on fertility, the committee recommends no classification of the insoluble nickel salts, due to a lack of appropriate data
  • for developmental toxicity, the committee recommends not to classify the insoluble nickel salts due to a lack of appropriate data
  • the committee is of the opinion that a lack of appropriate data precludes the labelling of insoluble nickel salts for effects during lactation.
On request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates the effects on the reproduction of substances at the workplace. The Health Council’s Committee for Compounds Toxic to Reproduction recommends to classify compounds toxic to reproduction according to the Directive 93/21/EEC of the European Union. In the present report the committee has reviewed β-chloroprene.

The committee’s recommendations are:

- For effects on fertility, the committee is of the opinion that a lack of appropriate human data precludes the assessment of β-chloroprene for fertility and sufficient animal data show that no classification for effects on fertility is indicated.
- For developmental toxicity, the committee is of the opinion that a lack of appropriate human data precludes the assessment of β-chloroprene for effects on development and sufficient animal data show that no classification of β-chloroprene is indicated.
- For effects during lactation, the committee is of the opinion that due to the lack of appropriate data β-chloroprene should not be labelled.
Trichloroethylene


On request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates the effects on the reproduction of substances at the workplace. The Health Council’s Committee for Compounds Toxic to Reproduction recommends to classify compounds toxic to reproduction according to the Directive 93/21/EEC of the European Union. In the present report the committee has reviewed trichloroethylene.

The committee’s recommendations are

- For effects on fertility, the committee recommends not classifying trichloroethylene on the basis of a lack of sufficient human data, and sufficient animal data which show that no classification is indicated.
- For developmental toxicity, the committee recommends classifying trichloroethylene in category 2 (substances which should be regarded as if they impair fertility in humans) and labelling trichloroethylene with T;R61.
- For effects during lactation, the committee is of the opinion that due to a lack of appropriate data trichloroethylene should not be labelled.
Diethyleneglycol (mono)alkylethers

Diethyleneglycol (mono)alkylethers are mainly used as solvents or intermediates. On request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates the effects on the reproduction of substances at the workplace. The Health Council’s Committee for compounds toxic to reproduction recommends to classify compounds toxic to reproduction according to the Directive 93/21/EEC of the European Union. In the present report the committee has reviewed the following three Diethyleneglycol (mono)alkylethers: diethyleneglycol (mono)methylether, diethyleneglycol (mono)ethylether and diethyleneglycol (mono)n-butylether.

The committees recommendations are:

- Diethyleneglycol (mono)methylether (DEGME)
  - For effects on fertility, the committee recommends not classifying DEGME on the basis of a lack of appropriate human data and sufficient animal data which show that no classification is indicated.
  - For developmental toxicity, the committee recommends classifying DEGME in category 2 (substances which should be regarded as if they cause developmental toxicity to humans) and labelling DEGME with T;R61.
  - For effects during lactation, the committee is of the opinion that due to a lack of appropriate data DEGME should not be labelled.

- Diethyleneglycol (mono)ethylether (DEGEE)
- For effects on fertility, the committee recommends not classifying DEGEE on the basis of a lack of appropriate human data and sufficient animal data which show that no classification is indicated.
- For developmental toxicity, the committee recommends not classifying DEGEE on the basis of a lack of appropriate human data and sufficient animal data which show that no classification is indicated.
- For effects during lactation, the committee is of the opinion that due to a lack of appropriate data DEGEE should not be labelled.
- Diethyleneglycol (mono)n-butylether (DEGBE)
  - For effects on fertility, the committee recommends not classifying DEGBE on the basis of a lack of appropriate human data and sufficient animal data which show that no classification is indicated.
  - For developmental toxicity, the committee recommends not classifying DEGBE on the basis of a lack of appropriate human data and sufficient animal data which show that no classification is indicated.
  - For effects during lactation, the committee is of the opinion that due to a lack of appropriate data DEGBE should not be labelled.