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# **Health Council of the Netherlands Reports 1999**

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Executive summaries



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No. A00/??, The Hague, ?????????? 2000

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Preferred citation:

Health Council of the Netherlands: Health Council of the Netherlands; Reports  
1999. The Hague: Health Council of the Netherlands, 2000; publication no.  
A00/??.

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ISBN: 90-5549-??

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## Preface

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The Health Council of the Netherlands (Gezondheidsraad) is the scientific advisory body on health and health care 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 1999. Copies of reports can be obtained from

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Menno van Leeuwen, MD, PhD  
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# Contents

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- Multiple chemical sensitivity *9*
  - Reconsidering the policy on HIV testing *11*
  - Laserpointers held up to the light *13*
  - Asbestos diseases: Asbestosis *15*
  - Adverse reactions to vaccinations  
in the national immunization programme 1996 *19*
  - Safety of amino acid supplementation *21*
  - Clinical genetic testing and counselling *25*
  - Screening and treatment of adolescents with schizophrenia *27*
  - Peak exposures to organic solvents *31*
  - Hormone disruptors in ecosystems *35*
  - 
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*Dit zijn conclusies en aanbevelingen die achter in het advies staan.  
Ik weet niet of het de bedoeling is dat die hierin komen???????????*

## Multiple chemical sensitivity

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Health Council of the Netherlands: Multiple chemical sensitivity. The Hague: Health Council of the Netherlands, 1999; publication no. 1999/01. ISBN: 90-5549-252-3 (Dutch/English)

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Of the 200 or so recent publications on MCS in the biomedical literature, only about 30 relate to original research. These publications are covered in table 1. In almost all cases, the validity and precision of the research leave much to be desired. This is related to the fact that there is no unambiguous definition of MCS, and hence, a priori, there is considerable vagueness concerning both the possible causes and effects of the phenomenon. If MCS is to be researched in a more scientific manner, there is need for hypotheses that are both reasonable and testable (Dye97). Researchers should agree on the measurable characteristics of MCS, as well as its possible causes. Because these are failing provocative research to determine the nature and causes of sensitivity in people with MCS complaints is without meaning and standardised research into possible ways of preventing the phenomenon is not possible.

Non-specific health complaints such as fatigue, concentration problems, headaches, respiratory difficulties and sore throat occur with great frequency. Clearly, these complaints deserve the attention of the healthcare services, some of whose members see a connection with exposure to chemicals. The issue at present is how far the current state of scientific knowledge justifies making such a connection, and whether people with the complaints benefit from a diagnosis of multiple chemical sensitivity.

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To label an environmental factor as the cause of a health problem, well-defined criteria need to be satisfied (see Hil65 and McC97 for example). The relation between the supposed cause and the health problem must be consistent and specific and the pathology must be seen to develop at an identifiable point in time between exposure and occurrence of the complaints. The existence of a dose-response relation is important, and the complaints must be biologically plausible. The degree of plausibility depends on the state of science. Observations should be coherent, and confirmed with positive and negative checks. Analogies strengthen the likelihood of a causal connection.

In the publications on complaints ascribed to MCS, these criteria have not been met. The relation between exposure to chemical substances and reported non-specific health problems is at best only associative. The existence of a clinically identifiable disorder, based on a reproducible mechanism, has not been proved. However, it is a fact that all kinds of environmental factors can cause different reactions in different people: one person can tolerate a factor without any problems; another experiences health complaints. Various factors and mechanisms play a role in this. People with the complaints, however, enjoy no benefit from all these types of phenomena being lumped together under a single label. A single label can confuse the situation, and makes it difficult to introduce appropriate environmental measures or treat the individual in question.

The conclusion has to be that current knowledge provides no medical scientific justification for the existence of multiple chemical sensitivity as a syndrome or disease. This conclusion does not reduce the importance of the assessment of the possible relations between combined exposures and the occurrence of health complaints.

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# Reconsidering the policy on HIV testing

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Health Council of the Netherlands. Standing Committee on Infectious Diseases and Immunology. Reconsidering the policy on HIV testing. The Hague: Health Council of the Netherlands, 1999; publication no. 1999/02. ISBN: 90-5549-253-1 (Dutch)

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In this report, a Health Council Committee examines the question of whether the new possibilities for treating HIV infection have implications for policy on HIV testing.

The policy on HIV testing in the Netherlands is characterized by a spirit of reserve which is partly the result of recommendations issued by the Health Council. In recent times, combination therapy consisting of one protease inhibitor and two replication inhibitors (otherwise known as triple therapy or ‘highly active antiretroviral therapy’ (HAART)) has been shown to be effective in the treatment of HIV infection. This affects the balance between the advantages and disadvantages of testing for HIV: in general the benefits now outweigh the drawbacks. The Committee is in favour of a more active testing policy and has arrived at the following recommendations.

- An active HIV-testing policy should be implemented with regard to pregnant women. By means of a few simple questions, the healthcare professional concerned should establish whether the woman in question belongs to a high-risk group and, if this is the case, offer the possibility of an HIV test. The test should also be offered in cases where risk status is uncertain.
  - In cities with a relatively high prevalence of HIV infection (such as Amsterdam and Rotterdam), a study should be carried out to compare the benefits of the risk-based approach outlined above with a general screening programme of all pregnant women for HIV-infection. The Committee
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advises against general screening at present due to the low prevalence of infection.

- HIV tests should also be offered to all individuals who belong to a high-risk group. This includes individuals who:
    - have or have had a partner who is HIV-positive
    - have used intravenous drugs since 1980, particularly those who have shared syringes or needles
    - have lived since 1980 in an area where AIDS is endemic (e.g. Sub-Saharan Africa and the Caribbean) or individuals who originate from these areas
    - have undergone an invasive medical procedure since 1980 in an area where AIDS is endemic
    - have had a transfusion with blood or blood products between 1980 and June 1985 or after 1980 in countries where blood is not routinely screened for HIV antibodies
    - have or have had a large number of sexual partners
    - have or have had a bisexual partner
    - have or have had a partner from one or more of the groups indicated above
    - and men who have or have had sexual contact with other men.
  - The Committee sees no reason to alter the present policy of reserve with regard to medical examinations for insurance purposes.
  - In accordance with the Medical Treatment Agreements Act, the healthcare professional concerned should provide the patient with sound information about the HIV test to enable him or her to make an independent decision. In this regard, the Committee urges the relevant professional groups to devote a great deal of attention to training those in a position to offer the HIV test.
  - The Committee recommends that clear written information material be drawn up regarding the change in the position on the advantages and disadvantages of HIV testing.
  - Lastly, the Committee indicates that, in cases where an individual tests positive for HIV, the patient should be referred to a physician experienced in the treatment of patients who are HIV-positive or who have AIDS. This is of particular importance in the case of pregnant women who are HIV-positive: only treatment carried out by experienced experts in accordance with a protocol can minimize the risk of teratogenic effects.
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## Laserpointers held up to the light

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Health Council of the Netherlands. Laserpointers held up to the light. A risk assessment. The Hague: Health Council of the Netherlands, 1999; publication no. 1999/03E. ISBN: 90-5549-255-8 (English)

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For several years small hand-held lasers are available to the general public, for instance in pens, keychains, knives and creditcards. These small diodelasers emit red light with a power varying from 1-5 mW. Originally they were intended as pointer, replacing the traditional wooden stick in the lecture hall and during presentations. Because of their low price they are now sold as toys and can be found everywhere: on the street, in discotheques and in classrooms. These lasers are often labelled as class 3A according to the American ANSI classification system. According to the European system this should be 3B, implying that they are potentially dangerous for the eye.

Sufficiently high powered lasers can cause retinal burns. To avoid this, exposure limits have been formulated as of 1970. From the output power, aperture and divergence of the beam the nominal ocular hazard distance (NOHD) can be calculated. At greater distances the maximum permissible exposure levels will not be exceeded. For most laserpointers the NOHD is between 5 and 15 metres.

The exposure levels are based on  $ED_{50}$  for laboratory animals (an  $ED_{50}$  represents the exposure level at which 50% of the animals sustains a lesion). An analysis of the relation between these values and the exposure limits shows that the probability of permanent eye damage at levels around the limits is very low.

Several European countries, including the Netherlands, regard class 3A and 3B lasers to powerful for general us as laserpointers and suitable for professional

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use only. They prohibited the trade of class 3A and 3B laserpointers and the application of class 2 lasers in toys. In most cases these measures are based on case-reports of alleged eye damage. However, in the international peer-reviewed literature not a single case of permanent eye damage due to laserpointers could be found. A review among Dutch ophthalmologists also revealed no case of permanent eye damage.

Nevertheless, exposure at these low power levels can cause strong aversion reactions and temporary changes in visual sensitivity, flashblindness, dazzle, glare and afterimages. The level of nuisance depends on the output power of the laser, the ambient luminance level and the exposure duration. Unexpected exposures can give rise to dangerous situations, especially when the exposed is in a situation where full concentration is important, such as driving.

The enacted trade ban contributes to the reduction of misuse and nuisance. It also prevents that in the near future increasingly powerful laserpointers enter the market that can cause retinal damage.

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## Asbestos diseases: Asbestosis

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Health Council of the Netherlands: Committee on Asbestos protocols. Asbestos diseases: Asbestosis. The Hague: Health Council of the Netherlands, 1999; publication no. 1999/04. ISBN: 90-5549-254-X (Dutch)

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Asbestos is a silicon-containing mineral that began to be produced on a large scale around 1870, with the increase in the use of fire-retardant insulation materials. The beneficial properties of asbestos cement, also known as Eternit, were discovered around 1900. Asbestos use in the Netherlands increased sharply from 1930. At that time it became clear that asbestos can affect the health. The relationship between working in the asbestos industry and the formation of fibrous lung tissue, known as diffuse pulmonary fibrosis was demonstrated. A relationship to lung cancer was established after the second World War, and, in 1960, a link to malignant mesothelioma was established. Worries about the health effects of asbestos increased also in the Netherlands after 1970 and protective measures were progressively introduced in the asbestos processing industry. The publication of the Asbestos Decree followed in 1978. The storage and processing of asbestos were forbidden by law in the Netherlands in 1993.

Although everyone in the Netherlands has been exposed to asbestos, asbestos-related diseases are almost exclusively traceable to occupational exposure. The major asbestos-related diseases are malignant mesothelioma, asbestosis and lung cancer. The Health Council of the Netherlands has previously published an advisory report on malignant mesothelioma. The present advisory report is devoted to asbestosis.

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Asbestosis is a chronic disease in which clearance reactions following inhalation of asbestos fibres stimulate diffuse inflammatory reactions and cell growth, which lead to the formation of fibrous tissue in the lungs. The formation of fibrous tissue results in a severe loss of elasticity and the lung loses its ability to take up oxygen. This eventually results in shortness of breath, disability and death. Approximately half the patients with asbestosis die from a form a lung cancer.

### Asbestosis protocol

In this advisory report, the Committee recommends a protocol to establish occupational exposure related asbestosis.

The diagnosis is made in various stages, which involve successively demonstrating the formation of fibrous tissue in the lung, determining the degree to which the person affected has been exposed to asbestos occupationally, and how the disease could have developed as a result of this, and determining the severity of the impairment of the lung function caused by the formation of the fibrous tissue.

The first step is to ascertain the formation of fibrous tissue (diffuse pulmonary fibrosis) on morphological grounds, usually with the help of techniques used in X-ray diagnosis, such as the 'high-resolution computed tomography' scan (HRCT). Where available, a biopsy can also be used to confirm pulmonary fibrosis. However, the Committee rejects requiring a biopsy specimen for this because it would involve unjustifiable surgical intervention for a patient with asbestosis.

Once fibrosis has been demonstrated, the relationship to asbestos in the lung should be demonstrated by means of an occupational case history. In the Netherlands, owing to the extreme scarcity of historical data about occupational exposure to asbestos, it is unrealistic to expect to obtain a completely quantitative estimate of previous exposure to asbestos. The Committee therefore believes it is satisfactory to establish qualitatively that the person concerned has been occupationally exposed to an amount of asbestos that exceeds the exposure threshold value considered necessary for developing asbestosis. This can be ascertained by estimating possible total exposure on the basis of an occupational case history compiled with the aid of available historical exposure data from the

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Netherlands and abroad for a number of significant industries and occupations, and determining whether this exceeds the exposure threshold value. The Committee concludes on the basis of epidemiological research data from abroad that the exposure threshold value corresponds with a minimum exposure of five fibre years. In addition, the sick person's exposure to asbestos must have started at least fifteen years before the manifestation of the disease. The severity of the disease is classified according to the system of the European Respiratory Society.

If the occupational case history provides insufficient data and a biopsy or a bronchoalveolar lavage (BAL) is available, the conclusion that there is asbestosis can also be reached by establishing that the cause of the fibrosis lies in the presence of asbestos fibres or asbestos particles in the lung. If no biopsy is available, this can be achieved by assessing the result of a bronchoalveolar lavage. However, it must then have been established that the person concerned has worked in an occupation or industry in which exposure to asbestos could have occurred and that the work was started more than fifteen years before the manifestation of the disease.

Lung function disorders must be established using standard lung-physiological techniques in laboratories that regularly perform examinations of this kind and that are certificated to do so on qualitative grounds. The Committee recommends ensuring that these centres are regionally distributed.

Because an increase in a lung function disorder may also occur after a long period, the Council recommends providing the possibility of a re-evaluation of the lung function disorder after three years.



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# Adverse reactions to vaccinations in the national immunization programme 1996

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Health Council of The Netherlands: Committee on adverse reactions to vaccinations in the national immunization programme. Adverse reactions to vaccinations in the national immunization programme 1996. The Hague: Health Council of the Netherlands, 1999; publication no. 1999/05. ISBN: 90-5549-258-2 (Dutch)

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At the request of the Minister of Health, Welfare and Sport, a Committee of the Health Council of the Netherlands analyses cases involving suspected adverse reactions to vaccinations carried out under the Dutch national immunization programme and reports on the matter annually. From 1996 onwards, the Committee has adapted its working method to a new assignment. The Committee now only assesses reports of severe or unusual phenomena or phenomena with lasting consequences. This selection is carried out by the National Institute of Public Health and the Environment (RIVM) in accordance with criteria formulated by the Committee. In addition, the RIVM publishes a report dealing with *all* suspected adverse reactions. This report is evaluated by the Committee.

In the year under review, a total of 42 suspected adverse reactions were presented for the Committee's consideration, including 14 cases from previous years which could not be incorporated in the Committee's previous reports. The Committee classified seven of these as severe reactions which could, to some extent, be related to a vaccination carried out within the framework of the national immunization programme: two involved local reactions, two general skin reactions (one of which with fever), one febrile convulsion, one breath-holding spell and one instance of thrombocytopenia. To the best of the Committee's knowledge, none of these reactions had a lasting effect other than a scar as the result of an abscess. Six deaths were presented to the Committee for consideration. In five of these cases, the Committee concluded that a causal

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relationship with the preceding vaccination was unlikely. The Committee was unable to make a judgement regarding the sixth death, as no postmortem examination results were available. However, had the Committee been able to confirm the clinical suspicion of cot death, this case would also have been classified as having no causal link with the preceding vaccination.

The Committee states that it has not encountered any previously unknown adverse reactions in the year under review.

At the time of the completion of this report, the first in the series of annual RIVM reports on all cases of adverse events following national immunization programme vaccinations, the report for 1994, had been made available to the Committee for evaluation. In the Committee's view, the report offers a sound basis for evaluating adverse reactions to vaccinations carried out under the national programme.

Out of a total of approximately two million vaccinations, the RIVM reported 590 cases of possible or probable adverse reactions. As far as can be determined on the basis of present knowledge and experience, all of these reactions were temporary in nature and not harmful in the long term. In view of the role played by the immunization programme in preventing a large number of cases of serious illness, the Committee regards the scale of the adverse reactions as fully acceptable. The Committee considers the adverse reactions reported by the RIVM and by the Committee itself as no reason for making changes to the national immunization programme.

The Committee recommends that:

- the guidelines with regard to the national immunization programme should be carefully observed
- in cases of sudden and unexpected death, a multidisciplinary examination should be carried out in accordance with the current protocol (Gen92)
- all serious and unusual adverse events following vaccinations, regardless of whether a causal link is thought to be present, should be reported to the National Institute of Public Health and the Environment\*, together with as complete a description of both symptoms and medical history as possible. This also applies to adverse events which are not or are no longer regarded as contraindications or are considered to be 'known'.

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\* National Institute of Public Health and the Environment (RIVM), Laboratory for Clinical Vaccine Research, Bilthoven, the Netherlands tel +31 (0)30 2742424, fax +31 (0)30 2744430

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## Safety of amino acid supplementation

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Health Council of the Netherlands. Committee on amino acid supplementation. Safety of amino acid supplementation. The Hague: Health Council of the Netherlands, 1999; publication no. 1999/06. ISBN: 90-5549-257-4 (Dutch)

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The addition of amino acids to food and dietary supplements is prohibited in the Netherlands, with the exception of a number of highly specific applications. In response to the increasing demand for dietary supplements containing nutrients, including amino acids, the Minister of Health, Welfare and Sport and the Minister of Agriculture, Nature Management and Fisheries requested the Health Council of the Netherlands to report on the safety aspects of adding amino acids to food and dietary supplements.

Amino acids are the building blocks of protein, one of the components of all living organisms. Some amino acids also act as neurotransmitters or hormones, or as the precursors of one of these two groups. A healthy body can produce sufficient amounts of the following amino acids: alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamine, glutamic acid, glycine, proline and hydroxyproline, serine and tyrosine. Other amino acids have to be obtained from the food we eat. These are the essential amino acids histidine, isoleucine, leucine, lysine, methionine, phenylalanine, tryptophan, threonine and valine. In addition to the 22 substances cited above, this report also deals with the amino acids ornithine and citrulline. These are metabolites of the above-mentioned amino acids, and are not incorporated into proteins. They are formed in the intestines, the liver and the kidneys.

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The reasons for adding amino acids to food and dietary supplements are many and various. The use of cysteine and cystine, glutamic acid and glycine, together with several of their salts as *additives*, is permitted due to their technological or sensory characteristics. Another reason for adding amino acids is to improve the 'protein quality' of food. In some countries, including the United States, the addition of amino acids to improve 'protein quality' is permitted under strict conditions.

Transport systems, which are shared by the various groups of amino acids, mediate the absorption of amino acids from the gastro-intestinal tract and their uptake by organs and tissues. This means that amino acids can exert an influence on each other's transport and absorption. While it is essential that this factor be taken into account when assessing safety aspects, there is a lack of quantitative data in this area.

In 1992, a report entitled 'Safety of amino acids as dietary supplements' was published by the Federation of American Societies for Experimental Biology (FASEB). This report concluded that there was insufficient data available to evaluate the safety of amino acids as dietary supplements. There were some indications of adverse health effects associated with the use of individual amino acids, but it was not possible to identify a safe upper level of intake for any of the amino acids as dietary supplements. The Health Council endorses the conclusions of the FASEB report.

After examining recent literature on this subject, the Health Council found no information upon which to base additional conclusions. The Council has, nevertheless, elected to present maximum acceptable levels for the addition of amino acids to food (including dietary supplements). The Council has opted for a general approach, using the quantity of amino acids present in the amount of protein for women recommended by the former Nutrition Council — now part of the Health Council — as a basis for setting maximum thresholds. The Council subsequently verified that, using this general approach, none of the values obtained for the various amino acids (except methionine) are known (within the limits of published research) to produce adverse health effects. The values recommended in this report for the maximum daily intake of amino acids via supplementation or food enrichment are listed in the table below. It is anticipated that these quantities can be consumed, in addition to the regular diet, without causing adverse health effects. They apply to the general population. The use of extra amino acids should be discouraged in pregnant or lactating women, children below the age of 13, patients suffering from metabolic

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disorders, those taking certain medicines (such as MAO inhibitors) and individuals on low-protein diets.

Recommended maximum quantities for extra amino acid consumption via supplementation or foodenrichment.

amino acid	maximum (grams per day)
<i>essential</i>	
histidine	1,2
isoleucine <sup>a</sup>	2,9
leucine	5
lysine	3,7
methionine	not permitted
phenylalanine	2,6
threonine	2,3
tryptophan	0,6
valine	3,1
<i>non-essential</i>	
alanine	2,1
arginine	2,3
asparagine + aspartic acid	4,4
citrulline	?
cysteine	0,5
glutamine	5,5
glutamic acid	5,1
glycine	2
ornithine	?
proline	4,5
serine	3,3
tyrosine	2,5

<sup>a</sup> the Health Council recommends that the branched-chain amino acids (isoleucine, leucine and valine) not be taken separately; consumption should only be permitted in combination, using the proportions indicated in this table

? no maximum quantity can be specified



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# Clinical genetic testing and counselling

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Health Council of the Netherlands: Standing Committee on Genetics.  
Clinical genetic testing and counselling. The Hague: Health Council of the  
Netherlands, 1999: publication no. 1999/07. ISBN: 90-5549-259-0  
(Dutch)

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The regulations on clinical genetic testing and counselling in the Netherlands apply to “postnatal and prenatal chromosome, biochemical and DNA testing, the clinical removal of foetal material, advanced ultrasound scanning for foetal abnormalities and complex genetic counselling”. The regulations are designed to assure the quality and continuity of the procedures in question, which are regarded as a form of medical care.

Experimental research has increased the potential applications of clinical genetic testing considerably. As indicated in the Health Council’s earlier advisory report “DNA Diagnostics”, both the Human Genome Project and research into specific hereditary conditions have yielded a great deal of clinically relevant information. It should also be pointed out that diagnostic DNA tests, including tests for germline mutations, are not carried out exclusively as a basis for genetic counselling. Furthermore, the results of diagnostic biochemical tests are frequently not of a clinical genetic nature.

The regulations on clinical genetic testing and counselling have been successful in promoting high quality standards. In addition, the relevant professional associations have set up committees to monitor quality and raise quality levels. In the advisory report referred to above, the Health Council expressed its approval of the quality standards in clinical genetic testing. A report into clinical genetic testing commissioned by the Health Insurance Funds Council also drew a positive conclusion regarding the quality of test activities.

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Between 1990 and 1995, the number of requests for genetic counselling rose by 11 per cent a year. The annual rate of increase is soon expected to reach 15 per cent, as a result of the rapid rise in enquiries regarding hereditary forms of cancer. The associated increase in the number of DNA tests is likely to be greater: perhaps 20 per cent. However, demand for chromosomal tests and advanced ultrasound scans is expected to rise to a lesser extent: 6 per cent a year is probable. No quantitative increase is anticipated in biochemical diagnostic testing for clinical genetic purposes. The present number of clinical genetics centres is considered sufficient to cope with the forecast levels of demand.

The committee does not believe that it is necessary to revise the definition of the forms of care covered by the regulations on clinical genetic testing. It is also concluded that concentration of clinical genetic testing in university centres has contributed to continuity and quality improvement. This concentration should be maintained in view of the nature of genetic counselling.

In the light of recent developments in the field of clinical genetics, the committee makes the following recommendations:

- Genetic counselling and the associated test activities should continue to be concentrated in the nominated centres.
- The professional groups involved in clinical genetics should have responsibility for drafting and updating quality requirements; in this context, the government's role should be supervisory.
- Forecasts regarding the level of provision required in this field should take account of the rapid increase in demand for counselling regarding hereditary forms of cancer.

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# Screening and treatment of adolescents with schizophrenia

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Health Council of the Netherlands. Screening and treatment of adolescents with schizophrenia. The Hague: Health Council of the Netherlands, 1999; publication no. 1999/08. ISBN: 90-5549-262-0 (Dutch)

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Schizophrenia is a severe psychiatric disease characterized by changes in thinking, perception and behaviour that conflict with reality as experienced by other people. A period of social isolation, neglect of hygiene or blunted emotions sometimes precedes these delusions or hallucinations. Most patients suffer the first symptoms during adolescence. Schizophrenia or a related disorder occurs in approximately 0.5% of the population; combined with the disease's early onset and often chronic course, this leads to considerable economic and human costs.

Guidelines for treatment recently became available in the Netherlands. The antipsychotic drug treatment indicated in the guidelines generally results in an improvement, but the disease appears to be chronic in the majority of patients.

The cause of schizophrenia is unknown. Genetic as well as environmental factors appear to play an important role in the disease's occurrence. However, the actual genes involved in schizophrenia are not known. There is also a lack of clarity about environmental factors, except insofar as complications in pregnancy are known to slightly increase the risk. It is impossible to predict the course of schizophrenia; a statistical relationship exists between the severity and certain symptoms but this provides an inadequate basis for making predictions about individual patients.

Research into the possibility of predicting the occurrence of schizophrenia has shown that future patients generally display abnormalities in

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neuropsychological tests more often than control persons. These abnormalities are not specific for the disease and even occur relatively frequently in people who do not subsequently develop schizophrenia or related disorders.

Investigation of other abnormalities, for example by means of brain-imaging techniques, also failed to produce results that could be used to predict the occurrence of schizophrenia.

Research conducted elsewhere frequently showed a long period between the onset of the first psychosis and the start of treatment. In this advisory report 'first psychosis' means the first psychotic symptoms suffered by the patient, and not therefore the first diagnosis of 'psychotic' made by a medical practitioner. Some researchers assume that the duration of the period between the first psychosis and treatment affects the final result; however this assumption is contested. On average, the final result is worse, if there is a longer period before the start of treatment. However, it is not known whether this is a causal link. It may be based on a common social factor, for example, because patients with a poor prognosis are more likely to isolate themselves from the environment. A prospective study has started in Scandinavia that may provide a decisive answer to this.

Apart from the possible effect of early treatment on the final course of the disease, early treatment is also of direct importance for patients and their relatives in order to reduce the duration and severity of the psychosis and to limit possible damage to social relationships. However, there is a lack of data about the length of time between the initial psychosis and treatment in the Netherlands.

#### Conclusions and recommendations

- No characteristics are known that could form the basis for predicting with reasonable accuracy which adolescents are likely to subsequently develop schizophrenia or a related disease, such as schizophreniform or schizo-affective disorders. Research into the possibility of making such predictions has produced insufficient results. Moreover, investigation also leads to many false positives, i.e. people who will not subsequently develop the disease. Likewise, if a high risk is suspected on the grounds of heredity and behaviour, it is not possible to predict whether or when the disease will occur.
  - The publication by the Netherlands Psychiatric Association of guidelines on the use of antipsychotic drugs in the treatment of schizophrenic psychoses has addressed the need for guidelines on treating schizophrenic patients.
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- There is a lack of data on the average duration of the period between the onset of the first psychosis and the commencement of treatment in patients with schizophrenia and related disorders in the Netherlands, and on the nature of a possible link between the duration and course of the disease.

The report leads to the following recommendations:

- It would be highly inadvisable to conduct (trial) population screening, in view of the inability to predict the occurrence of schizophrenia and related disorders with reasonable accuracy, the burden any such prediction would place both on the people who eventually develop the disease and those who do not, and the limited likelihood of being able to have any therapeutic effect on the disease.
- In general, the guidelines recently published by the Netherlands Psychiatric Association on treating patients with schizophrenia and schizophreniform disorders should be followed.
- Research is required into the duration of the period between the onset of the first psychosis and the commencement of treatment in patients with schizophrenia and related disorders in the Netherlands; depending on the results of that research, measures (or further research) could be considered for influencing this duration.



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## Peak exposures to organic solvents

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Health Council of the Netherlands: Committee on Peak exposures to organic solvents. Peak exposures to organic solvents. The Hague: Health Council of the Netherlands, 1999; publication no. 1999/12. ISBN: 90-5549-269-8 (Dutch)

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Exposures at work to volatile organic solvents may cause chronic toxic encephalopathy (CTE), a disease characterised by brain disturbances, concentration loss, fatigue, mental inertia, headache, depression and irritability. Volatile organic solvents are a vast class of hydrocarbons, including oxygenated and halogenated compounds. Many of the solvents on the market are mixtures specially produced for the different outlets such as paints, inks, glues, cleaning agents and many others.

The occurrence of CTE was first described in Scandinavian literature for painters, car mechanics, metalworkers and workers in the boat building industry in the late 1970's. The biological mechanism explaining the relationship between solvent exposures and the development of CTE has not been elucidated. At present there is consensus among occupational toxicologists that chronic exposures to concentrations below the occupational exposure limits (OEL's) will not enhance the risk of developing CTE. This is in agreement with the results of the toxicological and neurotoxicological assessments made for the main components in organic solvents. Epidemiological studies on workers from the relevant professions often report experiences like 'feelings of drunkenness' directly following exposures to organic solvents. On this basis it has been hypothesised that repeated short-term high exposures (so-called peak exposures) may be an important factor in the development of CTE.

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In this light the State Secretary for Social Affairs and Employment requested the Health Council to report on the implications of peak exposure to organic solvent vapours, in particular in relation to the development of CTE, whether a limitation of peak exposure is necessary and whether there exists a generic methodology to determine short-term limit values that may assist in limiting the risks of peak exposures. The TNO Food and Nutrition Organisation was requested to report on latest developments in the literature on peak exposure and the development of CTE. The TNO report has been attached to the present report as an appendix. It provides relevant information on experiments with human volunteers, on epidemiological studies, on health effects with glue-sniffers, on animal studies, and on the occurrence of peak exposures to solvent vapours at work. In addition physiologically based pharmacokinetic modelling was carried out to describe the biochemical fate of four important solvent molecules in the human body (so called PBPK studies).

The overall conclusion in the TNO report confirms the premise that data that could explain specifically the relationship between peak exposures to organic solvent vapours and the occurrence of chronic neurotoxicological effects, including CTE, are not available. Occupational hygiene data show that peak exposures for solvent molecules do occur and the maximum concentration in the peaks sometimes are ten times or more the existing OEL limits. PBPK studies show the internal concentrations of a substance in blood and the brain follow the development of the external concentration with a certain lag-time. Information obtained on glue-sniffers indicate there could be a relationship between acute physiological effects immediately following sniffing of solvents from the glue and the development of chronic neurological effects. With glue-sniffers the health effects are much more serious than the CTE effects observed in workers.

The committee concluded there probably is a relationship between peak exposures to organic solvents and the development of CTE, however a biological mechanism explaining this relationship is not available. This assumption, however plausible, can neither be denied nor accepted on the basis of the available information. In case peak exposures clearly cause CTE it still is not clear whether the total dose or the maximum concentration determines the development of CTE. Further complicating factors in the interpretation of the available data are the complex composition of many solvents and differences in susceptibility of individuals to exposure to organic solvents. Notwithstanding the committee is of the opinion that peak exposures would provide an important additional source of exposure to organic solvents and its reduction may contribute to the reduction of the risk for CTE.

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The committee recommends to further specify the present guidance on short-term exposure in the guideline of the Labour Inspectorate:

- a peak exposure should be defined as the mean exposure over a period of 15 minutes
- a peak exposure above two times the OEL value should not occur
- within a peak exposure the maximum concentration should not exceed a value of ten times the OEL-value
- during a working day the number of peak exposures should be limited to only four and the interval between two peak exposures should at least be one hour.

The committee advises to study more closely the characteristic exposure patterns for solvent vapours in the different professions. Better understanding of the causes of CTE such as the development of peak exposures, could help the management as well as workers in preventing exposures. The committee is of the opinion that attention should be given to early diagnosis of symptoms of CTE among workers, to prevent further development of CTE. This may be important for those with a higher susceptibility. PBPK studies on the relationship between peak exposures and the biochemical fate of the components of a solvent mixture in the body fluids of the human body could help in understanding the mechanisms that may lead to neurotoxicological effects, including CTE.



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## Hormone disruptors in ecosystems

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Health Council of the Netherlands: Hormone disruptors in ecosystems.  
The Hague: Health Council of the Netherlands, 1999; publication no.  
1999/13. ISBN: 90-5549-270-1 (Dutch)

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In recent years effects on reproduction have been identified in a large number of animal species and these effects have been attributed to the influence on hormonal systems of certain substances that are present in the environment. The supposition has been expressed in various publications that such substances also have an impact on human beings. In 1997 the Health Council of the Netherlands reached the conclusion that this supposition has not been verified for the Dutch population. In this advisory report, the Health Council — acting upon the request of the Minister of Housing, Spatial Planning and the Environment (VROM) — describes the current level of knowledge on the effects of hormone disruptors on animal reproduction in Dutch ecosystems.

The Committee focuses primarily on substances that interfere with the sex-hormone hormone balance. It calls a given substance a hormone disruptor if it is capable of disturbing reproductive physiology. The Committee also considers the effects of substances on the thyroid balance, in view of the important role which this system plays in development and reproduction.

In order to chart the implications of hormone disruptors for the situation in the Netherlands, the Committee has conducted an inventory of the field research that has been carried out in this country. In addition, it has classified around 80 pesticides and substances of industrial origin according to their hormone-disrupting capacity in the Dutch environment. The presence and possible effects of a number of natural and synthetic hormones have also been

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surveyed. These substances are excreted in substantial quantities by humans and especially by livestock.

In contrast to the situation in humans, effects on animal reproduction have definitely either been demonstrated, or else they are likely, in Dutch ecosystems. The majority of studies relate to animals in aquatic ecosystems (including animals preying in these systems), with much less being known about the effects of these substances on animals that live on the land.

Intersexuality is prominent among the (possible) harmful effects that are associated with the presence of such substances in the water compartment. It is clear, for example, that certain species of snail which inhabit the coastal areas of the North Sea have, to some extent, been affected by a specific substance (tributyltin). It is not known what impact this has on populations of different species that are present in the food chain, and thus on the functioning of the ecosystem as a whole. Unfavourable phenomena have also been identified in fish, which are attributable to the impact of hormone disruptors. What remains unclear, however, is precisely which substances are involved and the scale of the effects in question. According to British research, there is a link between intersexuality, which has been discovered on a large scale in certain fish populations, and the occurrence of increased levels of a specific protein (vitellogenin) in male fish. Such increases point to an oestrogenic effect caused by substances that are present in the environment. Based on research in our country, although as yet limited, it also appears that an increase of vitellogenin in male fish is occurring in the Dutch estuaries.

According to the Committee, there is sufficient evidence of the negative effects of DDE, PCBs and dioxins on reproduction in certain species of fish-eating birds and (marine) mammals. These effects have — especially in the past — led to a decrease in (local) populations. The environmental concentrations of these substances — especially in sedimentation areas of the Rhine, Meuse and Scheldt rivers — are still so high that an adverse impact on the reproduction and development of resident fish-eating top predators can still be expected.

The Committee designates 34 of the 80 or so pesticides and substances of industrial origin in the Netherlands as (potential) hormone disruptors. These are alkylphenols, organochlorine, organobromine and organotin compounds, phthalates and triazines. Some of these substances — for example, the organochlorine compounds — have mainly been used in the past, while in other cases usage — and therefore dispersion in the environment — is more recent.

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Examples of the latter category are the persistent organobromine compounds, which have already penetrated deep into the food-chain in the oceans. For the majority of substances, data are only available about mammals. For these substances it is therefore impossible to verify the extent to which xenobiotic substances play a role in aquatic animals and invertebrates.

The Committee also regards some natural and synthetic oestrogens as hormone disruptors. These substances are excreted in substantial quantities by humans and, in particular, by livestock and find their way into the surface water by a process of leaching and via sewage treatment plants. The concentrations of these extremely potent hormones in the major rivers are, broadly speaking, sufficiently high to give rise to effects on aquatic animals. In this regard, the Committee points out that it is likely that even higher concentrations of natural hormones occur in surface waters in areas of intensive livestock production.

According to the Committee, there are sufficient scientifically founded grounds for concern over the presence of substances — especially in the aquatic environment — which are capable of disrupting the sex-hormone balance in organisms and which might therefore pose a threat to the continued existence of species in ecosystems. In some species, effects on individuals and populations have actually been demonstrated, or else they are likely. Precisely what implications this has for biotic communities and entire ecosystems is unknown. However, because only very limited research has been carried out into the effects of the hormone disruptors that are present in the environment, it is quite possible that hormone disruption is more widespread than appears from the present report. It is precisely because many substances have been investigated in recent years for their hormone-disrupting action that this list has already grown considerably. Given the large quantity of substances that stand to be investigated over the next few years, it is reasonable to suppose that the number of substances that can be labelled as (potential) hormone disruptors will continue to rise substantially.

In this connection it should also be borne in mind that the Netherlands occupies a unique position in Europe as far as the presence of hormone disruptors in the environment is concerned. Various European rivers bring hormone disruptors into the Netherlands. Because the Netherlands is a sedimentation area, it is precisely the persistent hormone disruptors that remain in the sediments. This country also has an extremely intensive agriculture industry which uses various substances that (possibly) exhibit hormone disruptive effects. Account also needs to be taken of the presence in this small

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country of natural hormones as a result of its large numbers of humans and, in particular, livestock.

The Committee recommends that the monitoring programmes should be focused primarily on the water compartment and on manure. As far as the natural hormones are concerned, maximum priority needs to be given to small ditches and manure. Of the other substances, attention needs to be focused principally on the 34 substances which the Committee has classified as (potential) hormone disruptors, with the exception of a number of the organochlorine compounds, for which a successful policy has already been implemented. In view of its conclusion that little field research has been conducted into the effects of hormone disruptors within ecosystems, the Committee advocates that those monitoring programmes that already exist should be extended.

The Committee concludes that the instruments that are already available for monitoring effects on the sex-hormone balance in animals — although limited — are, nevertheless, adequate. These instruments include, amongst others, age structure and sex ratios of populations, transplanted sentinels, *in vitro* tests and chemical monitoring. It recommends extending the existing monitoring programmes with some of these techniques. The Committee emphasises the fact that there is no proven approach and that monitoring requires an iterative process, involving interdisciplinary collaboration, whereby ongoing efforts are made to determine which approach is the most effective.

