
Multiple chemical sensitivity

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to

the Minister of Health, Welfare and Sport

the Minister of Housing, Spatial Planning and Environment

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Introduction

In recent years, there has been much discussion in the United States about a subject known as ‘multiple chemical sensitivity’ (MCS). The key question is whether MCS exists as a unique syndrome. If so, it would mean some people experience health problems because of sensitivity to multiple chemicals in their living environment. The 90s saw several international scientific conferences on this theme. Furthermore, research programmes were initiated by the National Institute of Environmental Health Sciences (NIEHS) and by the Centers for Disease Control and Prevention (CDC). Meanwhile, there are various ongoing court cases in the United States, involving massive liability claims against employers and the government. Until now, MCS has been less in evidence in the Netherlands and other European countries than in the United States (Ash95).

The Health Council of the Netherlands produced an overview of the current state of knowledge concerning MCS, by means of a literature study. This overview formed a starting point for the Council to discuss the MCS phenomenon and its significance for public-health and environmental policies. This report is the reflection of these findings.

Overview of the literature

2.1 Introduction

By means of on-line searching the domain ‘Biomedical Sciences’ was searched, using the terms ‘chemical sensitivity’ and ‘chemical sensitivities’. The search produced hits in 35 databases, the majority in Embase ‘74-9723 (EMZZ), Medline 1966-jul/P4 97 (Ed 970522), PASC 1984 to week 23/97 (PASC), Science Citation Index ‘87-wk 21/97, Toxline Pre 1965-9703 (EM) (TOZZ) and Biosis Previews ‘70-B99/I48. Based on complete titles and summaries, a selection was made and approximately 200 publications retrieved. Besides articles, they included symposia reports and letters. Publications describing original research are numbered in this text (Cu192¹ for example) and listed by these numbers in table 1, which includes summaries of the publications, together with comments.

This report provides an overview of what the different authors understand by ‘MCS’, the complaints listed in connection with it and their incidence, as well as the presumed causes and their working mechanisms.

The first piece on multiple chemical sensitivity (MCS) appeared in 1962. The author — T Randolph — believed that exposure to chemicals in the environment could lead to chemical sensitivity. His description of the core features of chemical sensitivity came down to the following:

- the health problems usually appear after chronic or acute exposure to (petro)chemicals, and can be physical or psychological;

- becoming used to specific chemicals after chronic exposure leads to a reduction in the health problems (adaptation);
- following a period in an extremely clean environment, the adaptation disappears, new exposure causes the health problems to return in more severe forms;
- once a person has become sensitive to a particular chemical, he or she suffers health problems from exposure to an increasing number of chemicals in the living environment;
- if exposure to chemicals in the living environment is avoided, the health problems may disappear.

Randolph covered more than just chemicals in his description, including known allergens such as fungi, pollens and food additives as well (Fie96b). It was only after Cullen (Cul87) produced a definition including criteria that the term MCS came into vogue. A wide variety of synonyms are used in the literature, such as environmental disease, universal allergy, 20th century disease, chemical AIDS and idiopathic environmental intolerances (Mil94). The overview here uses the term MCS as much as possible.

Following the appearance of Randolph's publication, a discussion arose, beginning in the United States, as to whether or not MCS exists as a separate definable disorder. Medical opinion was and is still divided on this issue. Doctors who accept Randolph's theory and regard themselves as clinical ecologists, but other medical professionals as well, see MCS as a new disease. Other medical professionals, however, do not consider MCS as a patho-physiologically definable disease. Some of them maintain that the health complaints from people who claim they suffer from MCS are mainly psychological in nature. Among those who consider MCS to be a separate disease, there exist different schools of thought concerning its causes. Some groups see exposure to chemicals as the cause. Others believe that MCS can also be caused by exposure involving alternative environmental factors (Bro95, Wad93).

In essence, the published descriptions of MCS describe the occurrence of health complaints affecting different organ systems, appearing and disappearing in connection with measurable exposures to very low concentrations of chemically non-related substances. They differ in the minimal number of organ systems involved (between one and three), and in the inclusion or exclusion of additional medical conditions (Ash97, Cul87). Cullen's criteria also include the requirement that there must be an identifiable exposure at the first onset of the MCS-complaints (Cul87).

2.2 People with complaints

Reports about MCS complaints come almost exclusively from the United States. In their overview of the literature, Fiedler and Kipen state that it mainly concerns women

between 30 and 50, with at least two years of secondary education (Fie97). According to Reed Gibson, the percentage of females with MCS complaints ranges from 70 to 81 (Ree93). According to Cullen, people with MCS complaints are mainly well-educated women working in the service sector (Cul87). Using data from patient registers, he discovered that people with MCS complaints were mainly women between 30 and 50, working in education or healthcare (Cul92¹). According to Kipen women named more compounds that caused complaints than man (Kip95²). Lax and Henneberger found that mainly women between 36 and 50, not working in jobs with many direct health risks, suffer from MCS according to Cullen's criteria (Lax95³).

A study by Meggs et al. showed that persons reporting chemical-sensitivity complaints came from all age, income and occupational groups, from various ethnic groups, and included men as well as women (Meg96⁴). The researchers describe chemical sensitivity as becoming ill from the odour of chemicals. MCS aside, Sick Building Syndrome, Organo Psycho Syndrome, asthma and the organic-phosphate syndrome are also classified under the heading of chemical sensitivity.

The literature also contains completely different specifications of other groups in which MCS complaints might occur. Ashford and Miller, for example, distinguish four groups that they claim have an increased risk of developing MCS: workers in industry (mainly men in blue-collar jobs, between 20 and 65); inhabitants, schoolchildren, and workers who all remain for extended periods in so-called tight buildings; residents of areas where there is water or air pollution; and people (particularly women, with an above-average income, between 30 and 50) who are exposed to certain chemical products indoors, such as pesticides, medicines and household products (Ash97). According to Brod and Miller people with MCS problems include blue-collar workers, office workers, housewives and children (Bro96, Mil94).

During a workshop of the Association of Occupational and Environmental Clinics, it emerged that there was no data on the incidence or prevalence of MCS (Res92). Other authors have confirmed this (Mil94, Wol96). According to Miller, the cause is the lack of an accepted definition of MCS (Mil94). Meggs claims that the number of people who are sensitive to chemicals is actually high, but that MCS as defined by Cullen occurs much less frequently (Meg95).

Ashford and Miller maintain that MCS has a relatively high incidence (Ash97). The National Academy of Sciences, too, claims (but with no foundation) that an increasing degree of chemical sensitivity could develop in approximately 15% of the population. Based on discussions with doctors, Mooser estimates that between 2% and 10% of the general population could suffer considerable disturbance to daily life as a result of MCS (Moo87). Cullen and associates, however, report that a study conducted at their clinic in Yale shows that MCS as defined by Cullen is very rare (Cul92¹). In the clinic's files on occupational and environmental diseases, they found only 49 cases of MCS between

1986 and 1991, while for the same period, there were 2710 persons diagnosed otherwise. From a telephone survey conducted among the rural population of North Carolina, Meggs and associates found a prevalence of self-reported allergies and chemical sensitivity of 35% and 33% respectively (Meg96⁴). Chemical sensitivity was defined very broadly: becoming ill after smelling the odour of chemicals.

Summarizing, one can only say that different authors arrive at completely different specifications for the groups that develop MCS complaints. Concerning the incidence, too, reports show extreme variations. There is no standardized data based on validated measurements.

Possibly one of the most striking features of MCS is that a multitude of complaints could occur in various organ systems. Complaints affecting the central nervous system, the airways and the gastrointestinal tract are mentioned the most often (Ash97, Fie97, JAMA92, Kil93, Meg96⁴, Ree93, Wol96, Wol97):

- *Central nervous system:* irritability, concentration problems, disorientation, loss of short-term memory, speech problems, crying fits, anxiety, palpitations, trembling, perspiration, muscle and chest pains, headaches, tingling sensations, nausea, fatigue, dizziness, fainting, depression, complete lack of energy, sleep disturbances, and other neural and mental disorders.
- *Airways:* wheezing, shortness of breath, rhinitis, irritation of the mucous membranes and a dry cough.
- *Gastrointestinal tract:* digestion problems, a bloated feeling, flatulence, diarrhoea, constipation, stomach pains and a burning feeling (acid).
- *Eyes, skin and mucous membranes:* irritation and eczema.

In contrast to normal medical practice, the description of the proposed syndrome characteristics lump together complaints, diagnoses and functional disabilities. They relate to widely different mechanisms and they require an individual approach. The reason why they should be connected is not clear.

In various overviews complaints are reported following a recognizable event, they can develop in a relatively short time (a few minutes) and can last several days (Ash97, Bro95, JAMA92, Ree93). An occurrence of exposure in the workplace is in some cases cited as the onset. After some time, complaints would appear following exposure to chemicals found in normal, everyday situations. Intolerances for food were also reported. However, there are no objective descriptions of the course of MCS based on standardized observations, nor are there any unambiguous definitions.

Clinical ecologists believe that there is originally sensitivity to one or two chemicals, but that this number keeps increasing until the person reacts to exposure to (practically)

all chemicals. (Wol96). However, this pattern, too, is not substantiated by follow up studies.

Miller reports the phenomenon of adaptation, the development of tolerance for chemicals (Mil94). Others refer to adaptation as masking. Following adaptation, exposure to chemicals normally results in an influenza-like condition, but no (longer) produces clear complaints. Once the exposure has stopped, de-adaptation, un-masking or de-masking should occur. Further exposure leads again to clear complaints. In relation to chemicals, this hypothesized mechanism is not supported by valid data.

Some authors suggest that MCS is the precursor to, or exacerbates, disorders such as rheumatism, cancer, migraine, asthma and arthritis (Fie97, JAMA92). This has not been demonstrated, however (Res92). Levin and Byers suggest that in most cases (85%), MCS is a self-limiting process (Lev92). If exposure to the substances reported as the responsible factors is avoided, then the complaints should disappear from most people within 18 months. But this progression profile does not rest on standardized research data either.

2.3 Supposed causes and working mechanisms

A great deal of research has been conducted into the likely causes and working mechanisms of complaints associated with MCS. Table 1 contains descriptions of the empirical research in this area, with brief commentaries. The research concerns:

- Substances. The effects of exposure to specific substances in specific concentrations, in particular petrochemical compounds, formaldehyde, solvents, resins, tobacco smoke, perfumes, detergents, pesticides, as well as to dry-cleaned clothing, new carpeting and building materials (Ash96, Cul92¹, Fie96b, Gri95⁹, Han90, Lax95³, Lez97³², Loh96²⁵, Meg96⁴, Mil94, Mil95a¹⁰, Pir97, Rea89a²⁷, Rea89b²⁸, Ree93, Ros92, Roux94⁸, Roux95⁸, Sal96, Sik95, Sim93¹⁹, Wel92⁷, Wol96).
- Sensitivity based on an immunological mechanism (Alt95, Bal95, Bro92, Bro96, Fie92¹⁶, Fie97, Heu92¹⁷, JAMA92, Kol85, Per95, Pir97, Spa94, Ter93b, Ter94, Two94), neural disorders (Bol96²³, Con92¹⁵, Fie92¹⁶, Fie96a²⁴, Mil95a¹⁰, Ove96²⁶, Sim93¹⁹, Sim94²¹, Sta90¹⁴), disorders of detoxification systems (Bro96, Spa94, Ter94), fungal infections (JAMA92, Wol95) and genetic predispositions.
- Personality characteristics (Alt95, Bel92, Bel96²², Dot88¹³, Dot94, Fie92¹⁶, Fie96b, Fie97, Hum96³⁰, Meg93¹⁸, Meg96⁴, Sik95, Sta93²⁹, Ter94, Wol96).
- Psychiatric disorders (Ber97, Bin97³¹, Bla93, Bro96, Buc94²⁰, Dav96⁵, Fie92¹⁶, Fie96a²⁴, Fie97, Mil95b, Sch87, Sim90⁶, Sim92⁶, Sim93¹⁹, Sta97).

Regarding research into the complaints and the pathogenic effects of substances, studies into MCS do not generally offer any new perspectives in comparison to studies into and risk evaluations of the effects of different types of exposure. This latter type of research has been used for years by the Health Council of the Netherlands to underpin health based recommended exposure limits. The studies into the other factors mentioned and into possible mechanisms have many failings generally, as mentioned in table 1. Based on these studies, it cannot be concluded that MCS is a distinct syndrome or a disorder in its own right.

Various overviews report that for persons with MCS complaints, there is no validated treatment (Alt95, Alt96, JAMA92, Sal96, Ter94). Nevertheless, clinical ecologists, in particular, apply various types of treatment to persons they diagnosed with MCS. The methods described are:

- avoidance of exposure, including periods in environmental units (Ash97)
- diets (Res92, Rog96¹²)
- provocative and neutralization treatments (Ash97)
- medicinal therapies (Fie96a²⁴, Lev92)
- supportive and behavioural therapy (Res92, Wea96)
- detoxification and heat treatments (Rea96¹¹, Ter93a)

Some of these treatments are radical and not without risk concerning mental and physical health. Moreover, it should be noted that none of the propagated or applied treatments have been evaluated by efficacy and safety studies. Therefore these treatments are not discussed in this report any further.

Table 1 Overview of original research into multiple chemical sensitivity (MCS)

authors and type of study	study design	study results	remarks
<i>profile and incidence of MCS symptoms</i>			
1 Cullen et al.; incidence and profile of MCS complaints (Cul92).	Description and comparison of characteristics of people with MCS complaints and controls, both obtained from the client register of an occupational environmental health clinic in Yale. (MCS-criteria according to Cul87).	Persons with the MCS-symptom profile were mainly women, relatively young and from a good social-economic background. The group was fairly small, and it appeared that low exposure to chemical substances is much closer related to MCS complaints than high exposure.	Restricted group of people from a single clinic.
2 Kipen et al.; incidence and profile of MCS complaints (Kip95).	Study of 696 people (with and without MCS) from a clinic for environmental and occupational diseases, the purpose being to develop a questionnaire to determine the presence or absence of chemical sensitivity.	People with MCS complaints as a group cited more substances as causing problems than other groups, but asthma patients produced the highest score. Women's scores were higher than men's, irrespective of the diagnosis.	Questions arise regarding the criteria for people with MCS complaints, as well as the combining of groups of patients who may or may not meet the criteria.
3 Lax and Henneberger; incidence and profile of MCS complaints (Lax95).	The study question sought to answer the following: how many people with occupational MCS were there in a particular clinic; what were the similarities and differences with other clients in the clinic; what were the types of exposure reported; and to what extent could the MCS criteria of Cullen and the questionnaire of Kipen be used; and how did the complaints progress.	Women especially report MCS complaints, often affecting the central nervous system, in connection with exposure to volatile organic compounds. The investigators have the impression that because of the correlation between exposure and complaints, MCS represents a separate diagnostic category.	Descriptive research, with no independent standard diagnostic measurements.
4 Meggs et al.; incidence (Meg96).	Research into the incidence of allergies and chemical sensitivity in rural North Carolina, by means of questions posed by telephone to a random group.	The incidence of allergies that emerged from this study (35%) agrees with the findings from other research. For example, skin tests reveal atopy in 30% of the population, and rhinitis in 31%. The chemical sensitivity that emerged from this study has a prevalence of 33%.	MCS is not distinguished from SBS, asthma or OPS. Moreover, partially answered lists of questions are also included. Selection bias in the choice of test subjects and substances.

authors and type of study	study design	study results	remarks
5 Davidoff and Keyl; profile of MCS complaints (Dav96).	Study of 4 groups of people with MCS complaints and a control group from the general population. The people in the 4 study groups worked in industry, had been exposed to organic solvents or organic-phosphate pesticides, or were persons with SBS. The persons from the general population were selected at random. The research was carried out by means of a list of questions submitted over the telephone.	The self-reported health of the 4 MCS groups was significantly worse than the control group. Comparing the 4 MCS groups to the control group, the tolerance to odours, allergens, foods, alcohol and medicines was significantly lower, whereas the chemical sensitivity was significantly higher. No noticeable psychiatric differences were found between the MCS patients and the control persons. Although MCS patients had high negative emotional scores, these appeared to be more closely related to the MCS than any psychiatric history.	The definition of MCS is not clear. No double-blind study.
<i>case studies</i>			
6 Simon (Sim90, Sim92a).	Study of workers in an aircraft factory where a new production process was introduced. The new process meant working with solvents and irritation-causing substances. The research was conducted by means of shop-floor measurements, psychiatric evaluations and physical examinations.	Many workers felt the situation in the workplace was unsafe. The prevalence of psychological morbidity was high in relation to community samples, but comparable with those generally found among patients. MCS cases more often had prior psychological disorders. These concerned anxiety or depression, coupled with somatic symptoms.	The purpose of the study was not clear in advance. The study group was biased because claims were submitted. There were neither healthy control subjects, nor control subjects from outside the company. Further study defects are the absence of a study question and a description of the statistical methods used, as well as the use of a very sketchy definition of MCS. The study provides no foundation for the conclusions.
7 Welch and Sokas (Wel92).	Description of 20 instances of SBS related to the emission of 4-phenylcyclohexane from new floor covering.	The physical findings were generally normal. Subjects did, however, report respiratory-passage problems, headaches, etc.	Descriptions with no controls, study question, research protocol or statistical analysis.
8 Roux (Rou94, Rou95).	Study based on an inquiry among 751 employees at a French company using resins in the manufacture of car accessories.	According to the investigators, the results show that occupational exposure to chemical substances can affect the respiratory passages and cause MCS.	The purpose of the study is not clear. There is no statistical analysis and correction for the effects of smoking. On some points, particularly exposure, the study is too sketchily described to form a proper opinion.

authors and type of study	study design	study results	remarks
9 Grimmer (Gri95).	Retrospective study of 30 cases of sensitivity to chemical odours.	People working in the chemical, laboratory, plastics, graphical, paint and varnish, photographic or metal industries exhibit neurological symptoms such as migraine in combination with atopy, allergic rhinitis and skin problems. Clinical tests, however, showed normal values.	No clear purpose and no study question. Only the description of several cases. No controls. No quantification of the exposure.
10 Miller and Mittel (Mil95a).	Retrospective study among self-identified MCS patients by means of a questionnaire. Two groups: one for which the onset of the complaints was related to exposure to a pesticide (OP), and one for which the onset was related to the remodelling of a building (RE). Hypothesis: For psychological causes, there are no differences between the two groups; for physiological causes, there are significant differences in nature of the complaints and severity.	The investigators conclude that the results point to a physical mechanism and that there are arguments against a somatoform disorder as the cause of MCS. Hypothesis: Pesticides (organic-phosphates and carbarnates) from the OP group and solvents from the RE group both inhibit cholinesterase, leading to the same symptoms but with different degrees of severity. The OP group showed twice as many cardiac and neurological symptoms as the RE group. The RE group showed twice as many occurrences of mucous-membrane irritation and headaches as the OR group. There were no differences in triggers or cognitive symptoms.	Descriptive study based on self-reporting, limited to exposure to pesticides and remodelling. Possible recall bias and self-selection by people who read MCS newsletters. No independent standard diagnostic measurements.
<i>treatment methods</i>			
11 Rea et al. (Rea96).	Study of 210 patients with MCS, receiving heat-purification therapy, physical therapy and nutritional supplements.	Measurements of several fysiological parameters supported the subjectively experienced positive effect of the therapy.	The study was conducted without controls. The definition of MCS is not clear, and no reasons are given for not measuring certain parameters in certain patients.
12 Rogers (Rog96).	Study of 160 patients who had been reporting various complaints for an unspecified number of years, following exposure to ordinary foreign substances. The study was conducted using a questionnaire.	Most patients reported an improvement after following the macrobiotic diet. In some, however, a worsening occurred.	Bias from patients and investigator.

authors and type of study	study design	study results	remarks
<i>studies into the mechanism causing MCS complaints</i>			
13 Doty et al.; study with various foci (Dot88).	Study of 18 people with MCS, recruited via advertisements in MCS newsletters and by doctors specializing in MCS, and 18 control persons. Tests: odour threshold, internal nose airflow resistance, pulse rate, blood pressure, respiratory rate and depression. Purpose of the study: To determine whether persons with MCS exhibit changes in the variables mentioned.	No indications of a reduced odour threshold in persons with the complaints. Increased internal nose airflow resistance was observed, however, depending on whether the exposure was to phenyl-ethylalcohol or methyl-ethylketone. In addition, methyl-ethylketone led to increased nose airflow resistance in both the study group and the control subjects. According to the authors the results of the study suggest that subjects in the study group had greater difficulty in breathing, and that this might have been related to several physical complaints. A relation was found to (mild) depression, but it was not possible to establish that this was a causal one. In subjects from the study group and the control group, the systolic blood pressure dropped after the odour test. The study group had a higher respiratory rate during the odour test.	The criteria for inclusion in the study group were limited, and the group was very small. Extremely heterogeneous control group. High degree of self-selection. Not corrected for investigator bias.
14 Staudenmayer and Selner; neurophysiological study (Sta90).	Study of 201 right-handed persons who were reporting to an allergy clinic. Hypothesis: MCS patients do not differ from patients suffering from psychological abnormalities, depression, anxiety, mood swings, phobias, panic attacks or insomnia. The measurements involved EEGs, EMGs, peripheral temperature and skin resistance.	In relation to control subjects, persons with MCS showed neurophysiological similarities in their EEGs and EMGs to outpatients with primary or secondary psychological symptoms.	No satisfactory definition of MCS; the selection of patients is dubious. No corrections for investigator bias.
15 Cone and Sult; neuropsychological research (Con92).	Study using air measurements, a complete battery of neuropsychological tests and tests of nerve conduction, of employees at a casino hotel where the use of a pesticide against cockroaches was the probable cause of health problems. Cholinesterase levels in red blood cells and	Air measurements provided no information. The cholinesterase tests on 24 employees revealed a significant reduction of the cholinesterase in red blood cells, in comparison to the general population. The reduction of the cholinesterase in serum was not significant. The 19 employees with longer-term complaints reported headaches, nausea, palpitations, tremors, amnesia, fatigue, depression, etc. The complaints were probably the result of acute, possibly chronic, exposure to a cholinesterase-inhibiting pes-	It is not clear how the cases were defined, nor the controls. Also unclear is the difference between MCS and Acquired intolerance to solvents. On the other hand, the study does provide a good example of a scenario in which a specific type of exposure in the workplace appears to cause MCS-like complaints combined with ob-

authors and type of study	study design	study results	remarks
16 Fiedler et al.; psychiatric and immunological study (Fie92).	Study of 11 patients (3 men and 8 women) from a clinic for environmental and occupational diseases, the subjects being selected according to the criteria of Cullen. Aim: To take an initial step towards answering the question of whether or not MCS patients form a separate diagnostic group. Physical, immunological, psychiatric and neuropsychological examinations were carried out.	No significant or consistent abnormalities in immunological characteristics. The findings offer no support for the theory that MCS arises from premorbid psychiatric disorders or from a form of anxiety. Persons reporting MCS did, however, conform to a profile for somatoformic disorders, hypochondria and hysteria. The findings point more to a cause of MCS in a dysfunction of the central nervous system than in the immune system. The relatively poor performance in the memory tests and the reported sensitivity to odours recall the findings for exposure to solvents.	Exploratory study of a small group.
17 Heuser et al.; study of the nervous system, respiratory passages and the immune system (Heu92).	Study of 135 patients selected from a private-clinic population, on the basis of EEGs, MRI, brain mapping, SPECT, lung functions, EMG tests, X-ray examinations of sinuses and immunological examinations.	In some patients reporting acute exposure, the investigators discovered changes in TA1 cells and antibody levels that were different from normal. The investigators concluded that persons with MCS complaints could be their own controls for the measurement of objective MCS markers.	There exists a possible investigator bias, since the authors themselves have MCS complaints. The criteria applied are not clear. There was no clear starting point for the complaints and no controlled exposure. Different subsets of persons underwent different examinations. No statistical analysis.
18 Meggs and Cleveland; ear, nose and throat disorders (Meg93).	Study of 10 persons meeting the criteria of Cullen, with the aid of a rhinolaryngoscope. The study was carried out using case histories, paying special attention to ear, nose and throat disorders.	All subjects exhibited abnormalities: oedema, excessive formation of mucous, reduced circulation through the mucous membrane.	No hypothesis and no statistical analysis. Owing to the absence of control persons and the small size of the study group, no conclusions are possible.
19 Simon et al.; immunological and (neuro)psychological study (Sim93).	Study of 41 persons with MCS complaints and 34 control persons with chronic disorders of the locomotor system. Aim was to establish the role of immunological, psychological and neuropsychological factors in MCS complaints, using immunological measurements, standard measurements of anxiety, depression and somatization, as well as neuropsychological evaluations.	The findings are not supporting an immunological mechanism underlying MCS. Reduced ability to remember or concentrate was not confirmed by the neuropsychological tests. Psychological complaints, on the other hand, are a central feature of chemical sensitivity.	The definition of MCS is unclear and the criteria are limited.

authors and type of study	study design	study results	remarks
20 Buchwald; somatic, psychiatric and neuropsychological study (Buc94).	Study of persons with MCS complaints, chronic fatigue syndrome (CFS) and fibromyalgia (FM) from a CFS clinic and three private practices, using questionnaires and the Multidimensional Health Locus of Control.	No differences were revealed in the degree to which persons felt that they had the disease under control. Equally, no clear differences in demographic or clinical factors were revealed between groups. 80% of the FM and MCS persons satisfied the criteria for CFS. Complaints typical for one of the phenomena occurred just as frequently in persons with the other phenomenon. Only postexertional fatigue occurred significantly more often in the CFS and FM groups than in the MCS group; painful lymph nodes occurred more often in the FM group than in others. It is striking that the three groups did not differ in the self-reported effects of pollution, exhaust fumes or cigarette smoke. However, persons with MCS complaints scored significantly higher for the effects of gas, paint, solvents and perfumes.	It is unclear whether the study was a double-blind one. It is possible that investigator bias occurred. There was no control group of healthy persons or of persons with a disorder clearly different from MCS, FM or CFS.
21 Simon; neurophysiological study (Sim94).	Study of 6 Desert Shield and Desert Storm (DS) veterans, using brain scintigraphy, single photon emission computed tomography (SPECT), with the intake and evaluation being carried out by two experienced nuclear medical specialists.	The conclusion was that the pattern in the DS veterans was comparable to that of persons exposed to neurotoxic substances. This was not specific for particular substances.	The study was a limited case-control study. No description of possible exposure. There is no mention of the significance of differences between patterns.
22 Bell et al.; study carried out using psychiatric questionnaires and questions on atopy and autoimmune diseases (Bel96).	Study of 1000 students, with the aim of determining the psychological, neuropsychiatric and somatic characteristics of persons who report that they become ill from the odour of chemicals, or that they are sensitive to chemicals. The study was carried out using questionnaires, checklists with 28 questions on psychiatric, allergic and medical disorders diagnosed by a doctor, psychiatric questionnaires and a cacoscopia score.	Non-invalidating cacoscopia and chemical sensitivity both occur frequently in students and the rest of the population too. Sufferers from cacoscopia and chemical sensitivity differ in the following aspects: Sufferers from cacoscopia include more women than men. This difference does not exist between persons who are chemically sensitive and those who are not. Chemically sensitive persons have more atopic allergies and autoimmune diseases than persons who are not sensitive to chemicals; they are also more often left-handed. These differences were not observed between the cacoscopia and non-cacoscopia groups. Neuropsychiatric and somatic complaints occurred more frequently in cacoscopia sufferers than in other persons, whereas this difference	The only variables used were the sex of the subject, and the numbers (percentage) of cacoscopia and non-cacoscopia sufferers that considered themselves sensitive to chemicals. The selection of subjects was based on self-reporting. From the discussion, it emerges that the investigators were mainly interested in cacoscopia and only to a lesser extent in chemical sensitivity. The authors admit that psychology students are not representative of the general population and that the study area (southern Arizona) is probably not a representative zo-

authors and type of study	study design	study results	remarks
23 Bolla; neurobehavioural study (Bol96).	Study of 35 patients in a clinic for occupational and environmental neurology, the patients having been exposed to organic solvents and pesticides at home and at work. The study was carried out on the basis of the criteria of Cullen and made use of neurobehavioural tests. The aim was to establish if the cognitive functions of the subjects with MCS were restricted in comparison to the subjects from other groups.	The often-reported subjective MCS complaints are not confirmed in this study. This suggests that the functioning of the central nervous system of persons with MCS complaints is not affected.	Possible bias because the subjects presented themselves. In addition, the study group was small. Apart from the limitations mentioned by the authors, few remarks are necessary.
24 Fiedler et al.; psychiatric and neuropsychological study (Fie96a).	Study of persons with MCS complaints (with and without a clear onset) and CFS, with normal subjects as controls, the object being to determine the characteristics distinguishing MCS, CS and CFS from each other, and to observe the psychiatric and neuropsychological complaints of these groups in relation to the control subjects. The criteria used were those of Cullen, CDC criteria (Centers for Disease Control), the inventory questionnaire of Kipen et al., concentration, visuomotor and memory tests, lifestyle questions and neuropsychological tests.	Standardized psychiatric and neuropsychological tests showed no differences between the MCS and CS groups, and the group of persons with CFS. Differences did emerge, however, in the number of lifestyle changes and the number of substances that people reported as causing sickness. Subjects with CFS complaints reported more changes in lifestyle. Persons with CS complaints scored highest for existing and earlier psychiatric disorders. The majority of complaints of MCS, CS and CFS subjects in relation to the controls concerned depression and somatization. Complaints of neuropsychological problems were also present, but not different from those of the control subjects.	Comparative study of small groups, with some self-selection.
25 Lohman; neurological study (Loh96).	Study using the evaluation of data on 466 anonymous persons that had neurological abnormalities, some of whom had also mentioned MCS complaints.	Exposure to neurotoxic substances is not enough to cause MCS complaints. MCS complaints often occur together with CFS and atopy.	Within the limits stated by the investigators, the study provides some interesting findings. A causal interpretation is not possible. No statistical evaluation.
<i>animal models</i>			
26 Overstreet et al.; (Ove96).	Study into the possible use of a particular type of rat (Flinders Sensitive Line, FSL), specially bred to be (hyper)sensitive to diisopropylfluorophosphate (DFP), an organic phosphate, as an animal model for MCS patients.	FSL rats exhibit cholinergic sensitivity. Besides serving as a model for depression, they could also serve as a model for MCS patients.	This model could be used to study the etiology and mechanisms, provided the model could be validated. Limited to specific exposures.

authors and type of study	study design	study results	remarks
<i>provocative studies</i>			
27 Rea et al.; Environmental Control Unit (ECU) (Rea89a).	Study of 50 persons aged 21 to 61, with chemical sensitivity, using double-blind provocations in an environmental unit. Aim: To evaluate a test protocol in an environmental unit and determine if low concentrations of chemicals produce objective symptoms. Provocations were inhalatory. Substances used were ethylalcohol (<0.5 ppm), phenol (<0.0025 ppm), chlorine (<0.3 ppm), formaldehyde (<0.2 ppm) and the pesticide 2,4-D (<0.0034). Tests: lung function, skin temperature, limb strength and bruising, and pulse rate.	The conclusion of the investigators was that changes in the pulse could be used as an early objective test of chemical sensitivity. In only a very small percentage (10%) of the sensitive persons did the provocations cause an increase in pulse rate. Half of the subjects exhibited more serious complaints, and the rest exhibited none.	There were no control subjects, and the criteria used for chemical sensitivity are not clear.
28 Rea et al.; Environmental Control Unit (ECU) (Rea89b).	Study of 19 doctors with chemical sensitivity, using blood tests and an environmental unit. Study question: Is there a relation between chemical exposure in their medical practices and the complaints of the different doctors? Do the majority react to provocative substances?	After de-masking, the majority of subjects reacted to provocative substances. On admission, there were noticeable abnormalities in, for example, the number of T-cells in the blood. These disappeared during adaptation.	MCS criteria unclear. Description of a highly selected, small study group. Conclusions concerning MCS are not possible.
29 Staudenmayer et al. (Sta93).	A double-blind study of 20 persons (12 women and 8 men) diagnosed by clinical ecologists as suffering from MCS. Exposure took place in a controlled room, with the subjects wearing nose masks. Purpose of the study was to use a specially developed clinical algorithm to distinguish between verifiable chemical sensitivity and psychological abnormalities. An experiment to test the hypothesis for a particular substance was designed for each person separately, dose and length of exposure being dependent on the subject's medical history.	33.3% of the provocations induced reactions. Specificity was 64.7%, and efficiency was 52.4%.	The criteria for diagnosing MCS are not given, and no control subjects were included. Only those chemicals were tested that the patient knew or believed would cause a reaction. Dependent variables were restricted to reported subjective complaints. Conclusions about the group are not possible.

authors and type of study	study design	study results	remarks
30 Hummel (Hum96).	A double-blind study of 23 persons who met the criteria of Cullen for MCS. Purpose of the study was to show whether persons with MCS complaints responded differently after exposure to 2-propanol than to normal house air. Exposure was set at the odour threshold level (the value at which 50% of the control population can smell the odour). The study was conducted by measuring chemosensory event-related potentials (CSERPs) and by taking subjective measurements of the olfactory function.	The results imply that persons with MCS complaints might be sensitive to volatile chemicals because of modified chemosensory perception.	The study was done correctly. However, there was no control group, so that it is not clear to what extent the responses would occur in persons without MCS complaints.
31 Binkley (Bin97).	Study of 5 patients from a clinic for allergies and clinical immunology, to determine whether the patients had an underlying condition comparable to panic disorder, by the administration of a neurochemical stimulant. Psychiatric tests were also carried out, and distress measurements obtained by means of self-reporting.	All 5 patients showed signs of panic disorder following an infusion of sodium lactate. This substance causes complaints in 80% of persons with panic disorder, and in 20% of persons from a control population. The researchers conclude that MCS has a neurobiological basis similar to that of panic disorder.	The study was carried out without controls, on a very small number of patients. The value for general conclusions is very limited. No consistent definition of MCS was used (only self-diagnosis).
32 Leznoff (Lez97).	Study of 15 persons with MCS complaints, who had been referred by the Workers Compensation Board. Purpose of the study was to show whether the most commonly occurring MCS symptom complex was the result of anxiety-induced chronic or acute hyperventilation.	The investigators concluded that hyperventilating was the manifestation of an anxiety syndrome. This was triggered when subjects felt they had received an 'environmental insult'.	The study was conducted without controls, and all subjects received a different stimulus, which they could choose themselves. It is not clear who described the complaints and who evaluated them.

Summary and conclusion

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.

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 (see table 1). 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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A Motivation for the report

B Preparation of the report

Annexes

Motivation for the report

The statutory task of the Health Council of the Netherlands is to provide the Dutch government and Parliament with information about the ‘current level of knowledge relating to public health issues’ (Section 22, Health Act of 1956, revised 1997). The Council fulfils this by publishing advisory reports at the request of Government Ministers or of the Parliament.

Part of this task is to draw attention at an early stage to scientific developments that may have consequences for Dutch government policy. This report on multiple chemical sensitivity is intended as signposting on an issue that has lead to intensive discussion among scientists, particularly in the United States.

Preparation of the report

The literature study that was the basis of this report was done on behalf of the Health Council by HR van Yperen and ALM Rutten, both of BKH Consultants, Delft.

The report itself was prepared by Dr JAG van de Wiel, senior scientist with the Health Council.