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OF THE ENVIRONMENT
Environmental
Protection Agency

Multiple Chemical Sensitivity, MCS

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The reports are, however, published because the Danish EPA finds that the studies represent a valuable contribution to the debate on environmental policy in Denmark.

Contents

List of scientific terms and abbreviations

Agoraphobia	Fear of open spaces
ATSDR	Agency for Toxicological Substances and Disease Registry (USA)
Autonomic nervous system	Nervous system which cannot be controlled by the mind
C-fibre	Special nerve fibre of the olfactory nerve in the nose
Clinical ecologists	Physicians who practice according to clinical/ecological guidelines (environmental physicians)
Cognitive	Refers to the intellectual functions of the brain: Perception and preparation of sense impressions
Dysesthesia	Psychogenic hypersensitivity to external impressions
ECU (***Environmental Control Unit***)	Climate chamber for exposure experiments
Environmental physicians	American physicians who set up a holistically oriented disease model. Organised in the "***American Academy of Environmental Medicine***".
EPA	Environmental Protection Agency
GWS	Gulf War Syndrome
Haemoglobin	The substance giving blood cells their red colour
Homeostasis	The maintenance of a state of equilibrium, especially through physiological processes
Hyper reactive bronchi	Bronchi, which contract when cold air is inhaled
Hyperventilation	Exaggerated fast breathing during a longer period, which lowers the CO_2 concentration in the blood, leading to changes in the blood

	circulation in the brain
Iatrogenic	Of or relating to illness caused by medical treatment
Idiopathic disease	Disease of unknown cause
ILO	International Labour Organisation
Immune system	Defence system of the body against external organisms and substances
Interleukin	Special substance which is released by nerve cells during stimulation
MCS	Multiple Chemical Sensitivity
Neuroendocrine system	Interaction between the central nervous system and the regulation of the hormone balance
NIEHS	National Institute of Environmental Health Sciences (USA)
NIH	National Institute of Health (USA)
NIOSH	National Institute of Occupational Health and Safety (USA)
NRC	National Research Council (USA)
Nystagmus	Spasmodic eye movements caused by the balance organ being affected (see vestibular test)
Olfactory	Having to do with the sense of smell
Solvent poisoning	Acute: Temporary complaints of malfunctioning of the brain Chronic: Permanent symptoms of deteriorated cognitive brain function
Peer review	Quality assurance of scientific article in accordance with international rules and criteria for scientific research and documentation
Post-traumatic distress syndrome/disorder	Health complaints arising from a trauma
Somatic	Of or relating to the body, physical
T-cells	Sub-group of white blood cells (lymphocytes)
TILT	Toxic-induced Loss of Tolerance

Toxic encephalopathy	Chronic solvent poisoning
Trigger substance	Chemical which elicits complaints in low concentrations
UNEP	United Nations Environmental Programme
VDU	Visual display unit
Vestibular auto-rotation test (VAT)	Test of the balance organ in the inner ear
VOC	Volatile organic compound
WHO	World Health Organization under the UN

Preface

During the past several years, an increasing number of people have contacted the Danish Environmental Protection Agency (EPA) concerning symptoms experienced in connection with exposure to small amounts of chemicals, typically chemicals from various consumer products. The media have focused on the fact that certain individuals can be hypersensitive to chemicals.

Knowledge of why some individuals react violently when exposed to small quantities of chemicals, while others do not, is lacking. In many countries Multiple Chemical Sensitivity (MCS) has been on the agenda in the scientific community for many years, but not in Denmark. Medical science has been hesitant towards this new phenomenon and the extent of the problem in Denmark has not been investigated.

Consumers are increasingly being exposed to chemicals in the chemical products and goods of every-day life. Some people are apparently hypersensitive to exposure to low concentrations of a wide range of chemicals.

The incidence of non-specific symptoms in the population as a result of exposure to chemicals is uncertain. As a contribution to describing the problem, the Danish EPA has, as a start, initiated this project. The aim is to give a comprehensive account of existing knowledge and experience of MCS in Denmark and other countries. It will, hopefully, constitute a basis for a better understanding of MCS and for dealing with the problem in the future.

In Denmark, MCS is called odour and chemical hypersensitivity.

The technical part of the report has been prepared under contract with the Danish EPA during the period July 2001 – February 2002 by specialist in occupational and community medicine, doctor of medicine Martin Silberschmidt, ms ***consult.*** A steering group has functioned as technical sparring partner and source of inspiration. The steering group, which met twice during the project period, had the following members:

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Summary and conclusions

Chemicals are present in our daily environment in ever-increasing quantities, which cause some public concern. The occurrence of a new health disorder, where some people suddenly can no longer tolerate the odour of chemicals at doses far below those known to cause harmful effects, has caused even more concern. The condition referred to above is called Multiple Chemical Sensitivity (MCS), where a previously healthy individual experiences multiple, non-specific symptoms when exposed to chemical odours at very low concentrations.

MCS has received much attention abroad, especially in North America. In Denmark only little is known about MCS and the medical establishment has not shown major interest in the condition. In order to be able to fulfil the responsibility of proper environmental administration of chemicals, several uncertainties about MCS need to be answered. Can chemicals cause illness at low concentrations? What mechanisms cause people to become extremely sensitive to chemicals? What kinds of chemicals are involved?

This report gives a comprehensive review of the present state of knowledge and administrative practise regarding MCS in Denmark and abroad, and contributes hereby, hopefully, to a better understanding of the MCS problems.

The report is based on a study of the scientific literature, meetings, workshops and reviews, most of which are from the US. The practises of environmental administrations in European countries and in North America have also been registered.

MCS is a diffusely defined condition that can easily be confounded with other diffuse conditions because the symptoms of several conditions are very similar. Other conditions are fibromyalgia, chronic fatigue syndrome, sick building syndrome, Gulf War Syndrome and many more so-called environmental diseases.

The definition and tentative diagnosis of MCS is based on seven criteria (Cullen's criteria), which also help to distinguish MCS from other environmental diseases.

Typical cases of MCS have been observed in Denmark among people who have been exposed to organic solvents or pesticides at work. Only a few domestic cases are known, ***e.g.*** from indoor use of different products for surface treatment of woods.

In the US the majority of cases of MCS occurs in private homes and is due to exposure to indoor chemicals (VOC) and the extensive use of pesticides. There are several reports on MCS among workers from the US, Sweden and France. These are comparable to the Danish cases.

Prevalence studies from the US show figures between 0.2-6% in the general population. There are no prevalence figures for general populations in Europe. In a study of Swedish housepainters 30% had MCS.

So far there is no final proof of the causal mechanism of MCS. Some evidence on nasal inflammatory and neurosensory dysfunction, on neural sensitisation of the midbrain limbic system and on psychological mechanisms seems more convincing than the other proposed mechanisms, such as immunological, toxic loss of tolerance, somatization and conditioned response.

At this stage it seems most likely that MCS occurs more often in persons who are more sensitive to environmental stressors than others.

There is clear evidence from the epidemiological literature that MCS exists, even though the exact mechanism is not known and there are no demonstrable organic or functional changes.

The condition MCS is assumed to pass on in two steps: the initial phase with exposure often to a high concentration of a chemical substance, and the trigger phase – the subsequent set off of a number of symptoms by exposure to low concentrations of chemicals.

The administrative and preventive action regarding MCS in most countries is that of expectation for the final proof of the causal mechanism of MCS. In Denmark a joint action for preventing chemical gases in building materials may have contributed to a reduction of indoor air pollution in Danish buildings, which indirectly might have contributed to prevent some MCS cases. In Canada decentralised activities by the authorities with public participation for "no scent-policy" have been partly successful. The Swedish and German environmental and public health authorities are undertaking epidemiological studies on MCS at the present time.

A limitation of the risk for exposure to chemicals, both at high and low concentrations, seems to be the primary objective for preventing new cases of MCS. Avoidance of the initial exposure seems especially important, ***e.g.*** exposure to high concentrations of solvents after painting of big surfaces or to high concentrations of aerosols (***e.g.*** hairspray) in closed rooms.

The consumers should always know when and to what kinds of chemicals they are exposed to. Consumers can contribute to prevent the break out of MCS-symptoms by avoiding indoor exposure to high concentration of volatile chemicals and by avoiding use of strongly smelling products, including use of perfume and scented products.

Based on the information of this report the following attempts are indicated for reducing exposure to chemicals:

- Generally, limited use of chemicals in everyday life
- Limited use of volatile chemicals (***e.g.*** scents) and chemicals in the form of aerosols for personal and household use.
- Limited use of pesticides and biocides.

Special attention might be directed towards:

- Cosmetics, cleaning products and products for surface treatment regarding their use and content, and
- In-door air pollution from building materials and furniture as well as tobacco smoke and exhausts from traffic.

Preventive action for MCS could contribute to a better protection of all those exposed to chemicals, especially the most vulnerable groups. Recognition of the illness MCS would lead to a better understanding of MCS patients and their needs.

1 Introduction

The production and use of new chemicals and products have increased during recent decades. Chemicals, which can constitute a potential hazard to the environment and to people, are found everywhere in the environment.

Little is known about most chemicals with regard to their harmful effects and the regulation of substances often “lags behind”, since restrictions are usually based on new knowledge and experience of harmful effects. Better methods to solve this problem and make up for lost time are needed.

When a new chemical offers considerable socio-economic benefits, it is difficult to argue about health risks, which cannot be fully documented. The introduction of the precautionary approach has made it possible to give greater consideration to nature and health, even when detrimental effects are poorly documented (Beltram, 1998).

The problem presented above is also relevant in connection with health risks for a group of people who feel ill as a result of exposure to chemicals in very low concentrations – concentrations so low that they do not bother most people. This condition is called ***Multiple Chemical Sensitivity*** (MCS). Individuals with MCS can react to a large number of chemicals at concentrations that are far below those, which can result in toxic effects.

Toxicological studies during recent decades have shown examples of chemicals, which were injurious to health in concentration, but which had previously been considered “safe”. Some combinations of chemicals or a chemical in combination with another environmental factor can enhance the deleterious effect compared to the effect of the chemical or factor by itself (***e.g.***, asbestos and tobacco, organic solvents and noise).

These things should be studied in order to identify possible groups of people at risk and mechanisms behind the phenomenon, and also in order to establish the imperativeness of preventive measures and to decide on which measures to take. Most of all, the authorities need documentation for connections between exposure to chemicals or combinations of chemicals in low concentrations and the reported health complaints, before they can step in.

The existing documentation of MCS does not meet internationally agreed medical science criteria for recognizing a disease. The authorities have no basis for preventive action.

It is not foreseen that the disease will be recognized in the near future. Apart from patient organizations and the group of MCS-afflicted persons, few have dealt with MCS in Denmark.

1.1 About the report

The target group of this report is authorities and practitioners within the sectors of environment, working environment, and health.

The aim of the report is – broadly – to disseminate existing knowledge on MCS. The report is based on a review of scientific literature and recommendations from expert panels on MCS, and on enquiries to environmental and health authorities in several countries.

The report is to be a starting point and basis of evaluation for the Danish EPA in its future management in relation to MCS.

Definition of the task

The report is to shed light on the following:

1. the existence of objective documentation for MCS caused by chemicals in low concentrations,
2. the existence of documentation for mechanisms causing MCS,
3. chemicals and circumstances of exposure which are particularly relevant for Denmark in connection with MCS, and
4. opportunities of preventive action/protection.

The report gives a complete and up–to-date description of the problem, including as much essential information as possible in relation to MCS, but not to other environmental ailments.

The report is not a scientific paper. But the information given and the list of references are meant for scientific use in relation to MCS.

Scientific terms and abbreviations are listed after the list of contents.

1.2 Sources of information

The database Medline has 388 references from the period 1991-2001 on ***chemical sensitivity*** and ***multiple chemical sensitivity*****.** Several reviews and reports on the subject have also been produced during this period.

The most important sources of information used for this report are:

1. The European Union Directorate for the Environment (DG Environment) report ("European report", 1994 – not officially published),

2. ***Pre-decisional Draft Report on MCS*** (***US Interagency Workgroup on Multiple Chemical Sensitivity***) ("Interagency report", 1998 – not officially published),

3. ***Chemical Exposures. Low levels and high stakes***. (Ashford & Miller 2. ed. 1998),

4. ***A Review of multiple chemical sensitivity for UK HSE*** (***UK review***, Graveling 1999) "Graveling report",

5. ***Danish experiences in occupational medicine 1981-2001***

6. Literature until 2001.

This report is based mainly on the Interagency report and the Graveling report.

History, definition, name, and delimitation in relation to other syndromes

2.1 MCS, development history

The allergologist Randolph (1952) was the first to report on a group of patients in the US, who experienced symptoms from chemicals in their daily surroundings, both at work and in their homes. He assumed that their symptoms were caused by a stress reaction due to exposure to organic compounds such as solvents, petrol, perfume, exhaust gasses, ***etc***. Randolph and some of his colleagues published several new cases fitting to the description above.

The authors considered the illness to be a hypersensitivity reaction in accordance with the current broad definition of allergy of the 1950s and 1960s: An "intense" or "over"-reaction in one or more organs to an external stimulus, which in most people does not provoke a reaction. But many physicians and not least practicing allergologists and immunologists rejected this definition. They stuck to the narrower definition of the antigen-antibody-mechanism as (immunological) basis for hypersensitivity illnesses.

As a reaction to this rejection, Randolph, together with some like-minded colleagues, formed a new society for human ecology in 1965. He encouraged physicians of all medical fields to join the society. In 1985 the society became

the "***American Academy of Environmental Medicine***" (AAEM) and its members were called ***clinical ecologists***. The academy now has about 2000 members, 800 of which are oto-rhino-laryngologists. Even though the name of the academy includes concepts, which in Danish can be understood as environmental medicine, clinical ecologists from the US are not the same as Danish specialists in environmental medicine. Nor are environmental illnesses, which are diagnosed as such according to the definition of the AAEM, what Danish physicians regard as environmental illnesses.

In 1992 the academy presented their theory as a holistically oriented illness model for environmental illnesses, to which MCS belongs. According to this theory, many symptoms experienced by hypersensitive people arise from a functional disorder in one or more of the biological systems of the body (AAEM, 1992).

According to the AAEM, MCS has emerged because we are surrounded by an increasing number of potentially hazardous chemicals, which affect more and more people (see also Annex A).

The theories and concepts of the AAEM are described more thoroughly in section 6.6.

During the 1980s more and more accounts of MCS and other conditions and symptoms similar to MCS have emerged. The list of substances, which can elicit health complaints, has also grown considerably (see section 4.7).

Exposure to triggering causes can occur everywhere: In the home, at work, and out-of-doors.

Since 1990, MCS has been discussed increasingly in the US and Canada, among specialists as well as by the general public. The debate has included subjects as: MCS as a recognized illness, how it is defined and what causes it, the mechanism of illness, treatment, and the role of the authorities in relation to MCS. The unsolved problems relating to MCS have become more evident, ***e.g.***, through reference to them in the media and because MCS patients and their supporters have sought assistance from the authorities. Several ministries in the US government have been and are still involved in the debate, and they have funded a number of conferences and workshops.

Discussions concerning the ”Gulf War Syndrome”, which in many ways can be compared to MCS, have mobilised much support and many resources from high places in the US administration. In several US states and in some Canadian provinces MCS patients have been given compensation, and so-called ecological environmental health centres, where MCS patients are received and treated, have been established (see chapter 8).

Another historical perspective seems relevant as an introduction to this report. In a review article with many examples from history, Göthe (1995) describes how very different environmental factors for short periods of time have been

focal points for new concepts of illness, which have led to epidemic-like spreading.

Table 2.1 Examples of environmental illnesses, historic review from the 19th and 20th centuries (Göthe, 1995)

- 1830 writer's cramp when the quill was replaced by the steel pen
- 1850 arsenic poisoning from wallpaper, lamp shades, ***etc***.
- 1908 telegrapher's cramp when the telegraph was introduced
- 1920 amalgam – mercury poisoning, continued in 1970 and 1980 (Sweden)
- 1940 carbon-monoxide poisoning from generator gasses during the Second World War
- 1970 repetitive strain injury (Australia)
- 1970 VDU (visual display unit) related and electromagnetic illnesses
- 1970 illnesses from self-copying paper

Typical of the syndromes mentioned above is the fact that it has not been possible to detect objective functional or organic bodily changes. The symptoms are not specific and they resemble MCS symptoms. Most of the syndromes have disappeared in the course of a few years or decades.

2.1.1 Sensitivity in a toxicological context

Sensitive or sensitised people react more violently to a chemical when exposed to it a second time, than they did when they were exposed to it the first time. They also respond more violently at lower doses, which would not normally bother other people. Sensitivity is based on individual differences in susceptibility, where age, sex, genetic factors, other illnesses, previous exposure, and stress are decisive factors. In Denmark the word "intolerance" can be used instead of sensitivity.

2.1.2 Disease, illness, syndrome

Of the two English categories of sickness, d***isease*** (objectively measurable physiological and/or psychogenic change) and ***illness*** (a subjective state of discomfort which does not produce objectively measurable symptoms), MCS belongs to the latter. Some use the term ***syndrome***, which is a condition with several subjective symptoms (signs of illness) or discomfort.

2.2 Description of MCS

The description most often used is the following:

"***People who were previously well complain of repetitive non-specific symptoms which they ascribe to exposure to chemicals in very low concentrations.***"

MCS patients complain of good and bad odours. Odours originate from inorganic or organic chemicals.

2.2.1 MCS symptoms

The most frequently reported symptoms are listed in table 2.2.

Table 2.2 List of the most frequently reported MCS symptoms (Ashford & Miller, 1998)

Difficulty in breathing Pains in the chest Irritation of mucous membranes in eyes, nose, and throat Fatigue Complaints from stomach and intestines Pains in muscles and joints Skin complaints	Headache Dizziness Difficulty in concentrating Depression General indisposition Poor memory

Symptoms from various organs are shown in the left side of the table, and symptoms from the central nervous system (CNS) in the right side. According to the definition of MCS, all MCS patients have complaints from two or more organs. One of the organs is always the CNS. Many patients also show intolerance to alcohol (Vesterhauge, pers. com. 2001).

The reported MCS symptoms are not specific, that is they occur in connection with many other illnesses or syndromes.

2.2.2 MCS definition

The clinical definition of a disease is usually a combination of what the patient says and what an objective examination by a physician (physical examination) and laboratory analyses reveal. No objective changes are seen in connection with MCS. The definition of MCS is, therefore, solely based on observations made by the patient. They consist of the following criteria:

1. MCS starts in people who have previously considered themselves to be healthy.
2. The symptoms occur as a response to exposure to a certain chemical and they disappear, when this chemical is no longer present.
3. The patient complains of symptoms from more than one organ (two or more).
4. Symptoms can occur due to exposure to different non-related chemicals, which function via different toxic mechanisms.
5. It is possible to describe the situations of exposure, which bring about the symptoms.
6. Exposures, which bring about symptoms, involve very low concentrations; concentrations that are considerably lower than the average concentrations, which elicit health complaints in most people.

7. Other causes of illness can be excluded.

The bullet points listed above correspond to Cullen's (1987) criteria. These have been accepted by most of the international MCS scientists as the basis of common understanding and for co-ordinating further research.

Comments on the criteria:

According to several scientists, MCS starts after an **initial exposure.** This exposure can be a chemical exposure or a serious virus infection in an adult or it can be a traumatic event (Interagency, 1998; Graveling, 1999; Ashford & Miller, 1998). Some maintain that a psychogenic trauma can be the initial triggering event. This event is often a ***posttraumatic distress syndrome,*** which is a condition with symptoms of many different kinds following a serious accident.

It is important to underline that only few out of a group of people, exposed to the same chemical, develop the chemical sensitivity, which characterises MCS.

2.2.3 MCS, course

The condition lasts for several (more than two) years. Most people are never rid of the symptoms. Some patients experience symptoms daily. Others do so more rarely, perhaps once a week. A few have been found to lose their chemical sensitivity, enabling them once more to tolerate chemical odours in low concentrations.

Many patients react to an increasing number of chemicals and the number of symptoms also increase with time.

2.2.4 MCS synonyms

MCS has been given many names, especially in the English-speaking part of the World (see table 2.3). Most researchers use a name, which expresses their perception of cause, mechanisms or condition (result). The table gives a good representation of the differences and uncertainties in the perception of MCS among all groups dealing with the syndrome.

Table 2.3 Expressions describing conditions similar to *Multiple Chemical Sensitivity.* The names are grouped according to cause, mechanism and result in relation to the mechanism of illness *(from Ashford & Miller, 1998)*

Causal relations
Environmentally related illness Chemically induced enhanced susceptibility Chemically acquired immune deficiency syndrome (Chemical AIDS) The petrochemical problem

Mechanisms
Immune disease Immunotoxicity Immune dysfunction Immune dysregulation Acquired odour reaction Mass psychogenic illness Multiple symptom complex Toxic agoraphobia Idiopathic environment tolerance Multi-organ dysesthesia

Result
Multiple chemical sensitivity (MCS) MCS syndrome Chemical hypersensitivity syndrome Universal allergy Disease of the 20eth century Total allergy syndrome Environmental allergy or disease Brain allergy Environmental adaptation/difficulty syndrome Food and chemical sensitivity Toxic-induced loss of tolerance ("TILT") Scent antipathy

The condition has no official Danish name. In occupational medicine the term odour hypersensitivity is used.

A research team at the Copenhagen University Hospital (Rigshospitalet) has used the term ***acquired intolerance to organic solvents*** (Gyntelberg, 1986). In Sweden, the following names are used: ***multiple chemical hypersensitivity, multiple hypersensitivity, and environmental somatization syndrome*** (Ørbæk, 1998; Göthe, 1995; Lindelöf, 2000). In Germany MCS is called ***Chemikalienunverträglichkeit*** (chemical intolerance) (Maschewsky, 1998).

The ***American College of Occupational and Environmental Medicine*** is the forum in the US with most MCS experts. In 1999 it recommended the use of the name "idiopathic environment-related intolerance (IEI)" instead of MCS. The new name corresponds better with the present knowledge or lack of knowledge concerning the condition (ACOEM, 1999). Idiopathic implies that the cause of the illness is unknown. This is a better and more appropriate name.

During the last couple of years several scientists have adopted IEI or a similar name: ***idiopathic environmental illness (IEI).*** This is the most neutral name to date, which, however, can lead to confusion with other environmental illnesses (Sparks, 2000). MCS is used in this report because it is still the name most commonly used in the literature.

2.3 Delimitation in relation to other syndromes and illnesses

MCS is grouped among the so-called environmental illnesses. These include several syndromes presumably caused by stress factors in the environment, but which are not officially recognized as diseases. The term MCS is often used for different environmental illnesses. See the list of environmental illnesses in table 2.4.

Table 2.4 List of environmental illnesses somewhat similar to MCS

Fibromyalgia
Chronic fatigue syndrome (***Myalgic encephalomyelitis***)
Amalgam illness
Hypersentivity to electricity
Food intolerance (FI)
Sick Building Syndrome (SBS)
Gulf War Syndrome (GWS)

Many people complain of the same symptoms as in MCS, while the physicians cannot detect objective signs of illness. Unlike MCS, the other environmental illnesses are not caused by exposure to chemicals but possibly by other mechanisms.

MCS is distinguished from the other illnesses by the criteria defining MCS (see subsection 2.2.2). People fulfilling the criteria defining MCS must be considered as MCS patients, even if they also fulfil criteria defining other syndromes. A number of investigations show that some people fulfil the criteria defining several syndromes. Many people with SBS or GWS (see table 2.4) also fulfil the criteria defining MCS (see chapter 4).

The most important environmental illnesses, which can be distinguished from MCS, are described briefly below.

Chronic fatigue syndrome (CFS) and Fibromyalgia (FM)

These syndromes, which are also poorly defined due to lack of detectable objective changes, are not officially recognized. They resemble MCS in several ways. 40-to-50-year-old women with a long school education are over-represented among patients with these three syndromes (Buchwald, 1994). The odours, which elicit health complaints in 87-97% of the MCS patients, also elicit symptoms in 53-67% of the patients with chronic fatigue syndrome and in 47-67% of the patients with fibromyalgia. On the other hand, 75% of the MCS patients complain of pain in muscles and joints, which is typical of patients with fibromyalgia. There is every indication that these three illnesses are closely related. Some experts consider them to be one and the same.

Sick-building syndrome (SBS)

This syndrome covers a long line of conditions with different definitions of illness. According to the WHO, the main symptoms of SBS have to do with mucous membranes and the central nervous system, with or without relation to odours. Many SBS patients complain of symptoms, while few MCS patients do.

As opposed to MCS patients, SBS patients have no symptoms when they have left the building and are home or elsewhere.

Some SBS patients develop MCS. These are described in chapter 4.

Amalgam illness

In occupational medicine, poisoning from small doses of mercury has been recognized as a toxicologically based illness called ”micro-mercurialism”. Some of its symptoms are similar to those of MCS.

According to a theory from the AAEM, the mechanism behind amalgam illness is that a daily release of a small dose of mercury from amalgam tooth fillings can produce a condition similar to MCS. But numerous clinical investigations and experiments, especially in Sweden, do not confirm this theory (Stenman, 1997). Out of a number of persons, who were of the impression that their symptoms originated from amalgam tooth fillings, another illness was found to be the cause in 30% of the cases. These persons no longer had symptoms, when they were cured of the other illness (Langworth, 1997). An investigation in Finland has shown that among people with amalgam tooth fillings, a small number have a high concentration of mercury in their urine. In 4 out of 26 persons with amalgam fillings, all of which had a high content of mercury in their urine and symptoms of mercury poisoning, all symptoms disappeared with the removal of the fillings (Stenman, 1997). The Author is of the opinion that it has to do with a regular toxicological mechanism of illness.

Hypersensitivity to electricity

This environmentally based syndrome is of widespread occurrence in Sweden. Patients complain of symptoms when they are close to electrical appliances and installations. The symptoms resemble those of MCS. The mechanism is explained as electromagnetic fields affecting the bodily functions (Viby, 2001).

Many people in Sweden have been tested for hypersensitivity to electricity in clinics for occupational medicine, but no connection has been found between the alleged symptoms and electromagnetic energy. Since hypersensitivity to electricity has nothing to do with exposure to chemicals, this syndrome does not comply with the definition of MCS adopted in this report.

Food intolerance (FI)

Many physicians and scientist consider FI to be an illness component of MCS (Eaton, 2000; Rea, 1992). People with FI have experienced a chemical poisoning and later develop MCS-like symptoms when they eat certain foods. The mechanism is triggered from the gastrointestinal tract and is, therefore, not in accordance with the definition of MCS (Eaton, 2000).

A small group of people with FI have, however, developed odour hypersensitivity with MCS symptoms.

The mechanism behind FI is unknown and the syndrome is not recognized as a disease.

Porphyria

Some MCS patients have symptoms that are similar to those found in patients with porphyria,

which is a metabolic disorder affecting several organs: The skin, the nervous system, synthesizing of haemoglobin. Typical symptoms are dark urine, stomach cramps, and sun-rash. Specialists cannot find any connection between the two pathological pictures. The situation is that the same person is afflicted with two illnesses at the same time (Ziem, 1995).

It is striking that many porphyria patients also have MCS. But so far, no illness mechanism has been found in porphyria patients, which can explain the mechanism of MCS.

2.4 Comments

MCS is a syndrome with subjective non-specific symptoms, unclear underlying mechanisms, and many different names. MCS belongs to the so-called environmental illnesses, among which are other poorly defined syndromes with unknown causes and with symptoms resembling those of MCS. It is easy to get them mixed up or to take one for the other.

This report focuses entirely on MCS.

3 Conferences, workshops, and reports on MCS

3.1 Activities in the US

Since 1990 several governmental institutions have sponsored or co-sponsored measures aimed at supporting MCS research.

The following is a chronological presentation of the activities mentioned in the Interagency Report (1998).

3.1.1 Conferences, workshops, and expert reports

National Research Council (NRC) Workshop 1991

The US EPA had scientific experts from all relevant fields invited to a workshop, which was to formulate an MCS research program. The workshop had three working groups covering clinical research, exposure and diagnosis, and epidemiological research respectively (***National Research Council, 1992a)***.

In Annex B ***(Recommendations from NRC workshop 1991)*** is a list of recommendations from the working groups. The list includes all recommendations, which at that time were considered relevant and adequate if a final description of MCS and the mechanisms behind it was to be made.

Workshop on MCS 1991 ***Association of Occupational and Environmental Clinics*** (AOEC, 1992)

The AOEC, which represents the occupational and environmental clinics in the US, arranged a workshop with clinically oriented goals such as definition of illness, description of circumstances leading to illness, treatment strategy, and pathogenesis (illness mechanisms). The problem formulation and the recommendations from this workshop were within the scope of the NRC workshop (see Annex B).

Some of the recommendations have led to research activities, which are presented in chapter 6.

NRC report on immuno-toxicological bio-markers, 1992

This report from a sub-committee, which was set up during the 1991 workshop, consists of detailed recommendations concerning immunological research. This accentuates the focusing on research in immunological causal mechanisms at the beginning of the 1990s (***National Research Council, 1992b***).

Expert panel for MCS set up by the ***Agency for Toxicological Substances and Disease Registry*** (ATSDR)

In 1993 Congress granted US$ 250,000 for a workshop on chemical sensitivity at low chemical doses and other impacts which the ATSDR was to arrange. The grant was decided due to widespread public concern that chemicals from waste landfills and fields treated with pesticides could cause MCS.

The ATSDR established a panel, which was to advise the government concerning measures necessary to fulfil the wishes of Congress (ATSDR, 1994). The panel included representatives from universities, clinical medicine, public health, industry, MCS patients, and the government, as well as observers ("***outside*** ***experts***). The panel drew up a prioritised list of MCS projects called "***Clean sites***" (1993)**.**

The recommendations in the list were within the scope of the large research catalogue from 1991. A few of the recommendations were new and more action oriented, such as:

1. The establishment of an intersectorial committee for the development of training facilities for the members of the committee and for new members from other institutions, and

2. Methods for facilitating the attachment of MCS research to other ongoing projects and the development of database facilities for recording and treating the data attained.

These recommendations have still to be followed.

National conference on low-dose exposure to chemicals and neuro-biological sensitivity, 1994

This meeting was organised by the ATSDR under the 1993 mandate from Congress, as a direct consequence of the recommendations from the expert panel. The importance of the olfactory system in neurophysiological and psychological causal mechanisms and possible connections between psychological and immunological reactions were discussed. Some of these mechanisms are described and discussed in chapter 6.

Instead of a traditional final report with results and recommendations, Kipen (1994) has prepared an official status report with new recommendations, which focus on improving the still persisting lack of co-ordination and co-operation between scientists. He proposed that all scientists should accept to adhere to a common set of criteria and requirement standards regarding definition of illness, selection criteria, methods of examination, establishment of prevalence, and definition of risk factors.

The course taken by this conference expresses a shift in research from research into immunological illness mechanisms to other areas. It also shows that sufficient co-ordination among scientists concerning definition of illness and standardization of methods is still lacking.

Public survey by the California Health Service 1994

The 1993 ATSDR meeting also recommended the development of research methodologies for detecting risk groups among the wider public. The California health service received financing for this task and delivered a final report in 1996 (***California Department of Health Services*** CDHS, 1996). Questions concerning MCS had been incorporated into an already existing public survey program. The report recommends use of the questionnaire developed for this investigation as a basis for a new, more thorough study. Such a study was never made. Some of the figures on prevalence shown in chapter 5 are from this investigation.

Workshop on controlled exposure investigations 1995, ***National Institute of Environmental Health Sciences*** (NIEHS)

This workshop was arranged in New Jersey as part of a national program "***Superfund Hazardous Substances Basic Research and Training Program***", which is managed autonomously by each state. Funding came from the NIEHS, which is a unit under the ***National Institute of Health*** (NIH). The aim was to establish a multidisciplinary research program, still for the purpose of gaining

a clear understanding of the illness mechanisms of MCS. The participants had backgrounds in neurophysiology, immunology, epidemiology, toxicology, and biology.

The outcome was four main recommendations:

1. Clear criteria for the selection of subjects to be examined
2. Full control of standardized exposure studies (Until now, no exposure experiments have given positive results)
3. Incorporation of conditioned reflexes and neural sensitisation (these concepts are explained in chapter 6) in the assessment of controlled provocation tests
4. Incorporation of ***case-control*** design in epidemiological investigations

Conference on experimental MCS research 1996, ***National Institute of Environmental Health Sciences*** (NIEHS)

The conference involved the same team as the workshop mentioned above. Both clinicians and experts from theoretical research environments within MCS-relevant fields participated. Five working groups discussed the following subjects:

- Empiric procedures for studying toxic-induced loss of tolerance (TILT)
- Conditioned reflexes (Pavlov) and MCS
- Psycho-neuro-immunological mechanisms
- Neurogenic inflammation
- Neural sensitisation and "kindling" mechanism

The introductions from the five groups and all of the presentations have been published in a special issue of "***Environmental Health Perspectives***" (no. 105, supplement 2, 1997).

Annex C ***(Main proposals from*** the ***EOHSI/NIEHS conference)*** contains the main proposals from the conference. It is an operational follow-up to previous activities, written by experts who have met on numerous occasions during the past 6 years to discuss and formulate fields of research and priorities. The same demands concerning standardization and quality control and better co-ordination and ”listening to one another” in this interdisciplinary research group are put forward.

It was apparently the last meeting with nationwide participation in the US, which was entirely devoted to MCS.

Report to Congress on Research on Multiple Chemical Exposures and Veterans with Gulf War Illnesses, 1998

The House of Representatives commissioned the report. The report mentions a consensus conference on multiple chemical exposure as seen in the light of the reported cases of Gulf War Syndrome and MCS, to be arranged under the ***Centre for Disease Control,*** as well as a planned research project "***Chemical Mixtures in Environmental Health***". The results from this conference have not yet been made public.

3.1.2 The US – The intersectorial government committee: Interagency working group

The most prestigious intersectorial working group on MCS, which has been set up under the US Ministry of Health is the "***Interagency Workgroup on Multiple Chemical Sensitivity***". The working group has included representatives from national ministries and administrations and from environmental and medical science research environments. It has produced "***A Report on Multiple Chemical Sensitivity (MCS)*****",** which is now available as a ***Pre-decisional draft*** (Interagency report, 1998).

The report is aimed at politicians, civil servants, scientists and physicians dealing with MCS problems.

It is based on a thorough review of the scientific literature, of expert hearings, of previous and present actions by the authorities, and of recommendations on technology and strategy.

The main conclusion of the report is that definite proof of MCS as a distinct disease is still (in 1998) lacking. The recommendations constitute a continuation of the cited recommendations, which are shown in annexes B, C, and D.

Public hearing on the report

After being assessed by an expert panel, a non-official version of the report was subject to a public hearing. The 460 responses to the hearing have been summarized in a report (***Summary of Public Comments Received for the Multiple Chemical Sensitivity Report***, 2000, ***Center of Disease Control,*** Ministry of Health).

Comments were received from professionals in the health service, from private citizens with and without MCS, and from organizations. Public employees were the most positive towards the report, private citizens the most critical.

Critical comments:

- The participation of a representative of the chemical industry creates

grounds for conflicts of interest, which weakens the report as an impartial document.

- The report should also contain information from other government authorities and from clinical ecologists who treat MCS patients.
- The list of references is not complete.
- The report should also recommend ways of avoiding exposure.
- Professionals in the health service, authorities, employers, and the public should use the report.

Positive comments:

- The report is a good starting point for recognizing MCS in the future.
- The report summarizes the most important problems related to MCS.
- The report is an important tool for those working with MCS.

3.1.3 The attitudes of professional medical organisations to MCS problems

Several professional medical organizations have taken part in the debate on MCS. These include the academy representing the clinical ecologists (AAEM) and five organizations under the ***American Medical Association*** (AMA) (The most important comments are placed within inverted commas):

- The 1992 AAEM report presents an holistic model for the pathogenesis of all environmental illnesses, including MCS (see chapter 6).
- ***American College of Physicians*** (1989) "Environmental physicians performing provocation tests should define the illness, which they are examining and treating, and they should adhere to current criteria for experimental design, such as the blinding principle and documentation of procedures and results."
- ***American Medical Association*** (1992). "MCS should not be recognized as a clinical syndrome".
- AMA, ***American Lung Association***, US EPA, consumer organization (1995) "Suspicion of MCS demands a thorough evaluation of the medical history. The case must not be dismissed as a psychiatric disorder. The possible existence of psychogenic problems should be looked into and the need for an examination by a specialist, ***e.g.***, an allergologist or a lung specialist, should be assessed."
- ***American Association of Allergy, Asthma and Immunology*** (1997) "None of the many theories, which have been put forward, have been proven."
- Proposal from a consensus group consisting of 31 scientists and clinicians, all experts on MCS research and the treatment of patients (Archives of Environment Health, 1999), on a clinical protocol, see chapter 7.
- ***American College of Occupational and Environmental Medicine*** (1999) is the most competent medical body concerning MCS. The working group emphasizes the importance of the opinions of physicians for decisions on compensation and social matters. The members recognize that proof of a connection between environmental factors and the MCS mechanism is still lacking. Therefore, they find no scientific grounds for environmental intervention (investigations and regulations) for the purpose of reducing MCS frequencies. This does not, however, apply to problems of indoor climate.
  The ACOEM supports a bio-psychological illness model, whereby they support the hypothesis behind a complex illness mechanism consisting of both psychological and physiological factors.

All organizations agree it is important for physicians to show real empathy for and interest in MCS patients, and scientific results should be published in scientific journals using ***peer review***.

3.1.4 Comments

Many conferences and workshops have been arranged in the US during the period 1990-1998 with the aim of discovering the causal relations concerning MCS. But the cause and mechanism of MCS has still not been discovered. New professional high-quality proposals for research activities, which should produce more unambiguous scientific results, are continuously being put forward.

Annex D ***(Topic list of recommendations for MCS research)*** gives a list of the most important recommendations from the seven conferences mentioned above, arranged according to topic.

Topics recommended for research at most of the meetings are:

- Epidemiological studies
- Definition of illness
- Provocation tests.

Most of the recommendations were presented at the first conference in 1991. The following conferences rather seem to be repetitions of the same "MCS-rituals". It is surprising that all of the experienced scientists continued to arrange new workshops and conferences, in spite of the fact that in the end they were always forced to conclude that the previous recommendations had not been followed and no progress had been made.

Tremendous resources and many hours of research have been put into a national effort, the outcome of which apparently does not measure up to the investments.

3.2 Activities in Canada

A workshop on ***Environmental Sensitivities*** was arranged in 1990**.** A workshop on ***MCS and the relevance to psychiatric disorders*** was arranged in 1992**.**

The Canadian experts discussed issues relating to MCS in a wider context than was done in the US. They discussed the physical, social and economic problems of the patients and the impact of MCS on the system of treatment by the health service, on the social services, and on the workplaces.

The following recommendations were adopted:

A. An MCS patient must be assessed in the light of his/her daily functions rather than as a preparation for diagnosis.

B. Criteria for diagnosing MCS as a) possible, b) probable, and c) highly probable were established.

For a number of years, the Canadian environmental and health authorities have been dealing with several preventive initiatives against the private use of pesticides and the use of fragrances in public places. ***Health Canada*** (Canada's health authority) has tried to recognize MCS, together with two other environmental illnesses, in order to create possibilities for social compensation to the victims (see also chapter 8).

Comment

The Canadian system seems to accentuate social and prophylactic aspects in relation to MCS comprehensively, whereas in the US focus is set more narrowly on an objective system of diagnosis.

3.3 Activities in Europe

3.3.1 Report from the Environmental Directorate of the EU, 1996

An international group of experts was given the mandate by the Environmental Directorate under the European Commission (***DG Environment***) to investigate the circumstances concerning chemical sensitivity in selected countries, including Denmark, Germany, Sweden, Norway, Belgium, The Netherlands, Great Britain, and Greece (European report, 1994).

The report "***Chemical sensitivity in selected European countries: an exploratory study***" was produced by 11 scientists from Denmark, Germany, Greece and the US. The main author was N. Ashford, who has written the book "***Chemical Exposures***" together with Miller. The investigation concept and the formulation of the questions, which were posed to representatives from the nine countries, were based on the way of thinking in the US at that time. Few Europeans were familiar with this way of thinking at that time. The report has never been accepted and officially issued by DG Environment.

The report is based on information from single key persons in each country, who had collected information in their own country. The information from each country consists of answers to the same questions, and these can be grouped under exposure, information from patients, relevant investigations and research, and plans for the future.

The result presents rather haphazard and diverse pictures of the European countries, which cannot be compared to each other. This can be due to the way in which the material was collected. The questions are based on experience and knowledge from the US, ***i.e.***, concerning possible causal hypotheses and target groups. The questions may have been misunderstood, or they may have been put to the wrong people.

The report concludes that MCS-like situations occur in all European countries, although each country has ”its own” MCS cases with their distinct types of exposure and illness.

Denmark is said to have diagnoses of illness and chemical exposures, which are possibly similar to MCS. Some of the information from the report is shown in chapter 4.

3.3.2 Report to the British Health and Safety Executive (HSE)

The Institute of Occupational Medicine in Scotland was asked to review multiple chemical sensitivity. With Graveling as main author, five of the employees of the institute wrote a comprehensive report, which answers the questions:

1. Has exposure to chemicals, including pesticides, in very small doses been shown to produce symptoms in humans?
2. Is there any documentation that these symptoms are due to a physiological or a psychological process?

The report contains a very detailed and thorough review of the different hypotheses for illness mechanisms (Graveling, 1999). Although it does not give precise answers to the two questions, the authors conclude, on the basis of epidemiological investigations, that MCS is a reality.

3.3.3 Report from the British Society for Allergy, Environmental and Nutritional Medicine (BSAENM)

The ***British Society for Allergy, Environmental and Nutritional Medicine*** is made up of British physicians from several fields of medicine. They have produced a comprehensive report on MCS with strong emphasis on the clinical ecology illness model. The symptoms are connected to food allergy, and an allergic reaction with no apparent immunological traits is among the causal mechanisms mentioned. Several medical histories are discussed, of which some do not fulfil Cullen’s criteria (Eaton, 2000).

3.4 Activities under the UN / WHO

International Programme for Chemical Safety (IPCS) Workshop in Berlin 1996

One of the recommendations in the report from the European Commission was to arrange a conference for all European experts on MCS, with the aim of discussing the situation in Europe and planning a co-ordinated effort on information and research on MCS. As mentioned above, the report was never published and the EU did not follow the recommendations.

On the other hand, the IPCS (***International Programme for Chemical Safety***) under the WHO, ILO, UNEP and the German government arranged an international workshop in Berlin in 1996. Experts from the US and Canada and from a few European countries were invited to participate. A representative from the ***DG Environment*** also participated, as did several representatives from the chemical industry (***IPCS- report of multiple chemical sensitivities***, 1996).

The workshop compares to the meetings in the US mentioned above. The same experts from the US participated. A final document from the workshop has never been published, because the participants could not agree on the conclusions. 80% could not support the main conclusions.

The WHO has done nothing since this conference (pers. com. Dr. Younes, IPCS/WHO Geneva, 2001).

3.5 Conclusions

This section describes the scientific activities on MCS that the health authorities carried out with support from the US government. The proposals for MCS research projects shown must generally be regarded as being of high quality and relevant, and they can to a great extent be an inspiration to research in Europe/Denmark.

Relatively little has come out of the many research projects. The causal mechanisms of MCS have not been clarified entirely.

The report from the working group under the US government has not been approved officially and published.

MCS is not recognized officially as a disease, and no precise methods of diagnosis, examination, and identification of groups at risk exist. The clinical ecologists and the established physicians have not approached each other.

4 Examples of MCS

In this chapter, typical examples of cases of MCS that fulfil the definition criteria and progress in two phases, as mentioned in chapter 2, are described:

- A perceived initial exposure to a chemical in a major though not necessarily toxic dose
- A state with increased response from several organs to exposure to the same chemical in a lower dose and the development of symptoms in connection with exposure to other chemicals (trigger substances)

4.1 MCS after exposure to organic solvents

It is well known that exposure over many years to organic solvents can cause various injuries to the brain and other organs. It seems possible that MCS can also be caused by such exposure over a long period of time.

A report from the Clinic for Occupational Medicine and the Department of Oto-rhino-laryngology at the Copenhagen University Hospital (***Rigshospitalet***) (Gyntelberg, 1986) is one of the first publications dealing with such cases.

The author used the term "***Acquired intolerance for organic solvents"***. The investigation involved 50 persons who had developed a number of symptoms from different organs after exposure to low doses of solvents. These doses had not previously created symptoms. All persons had previously experienced acute solvent poisoning. 22 demonstrated toxic encephalopathy.

The most apparent symptoms in all persons were dizziness, nausea, and fatigue, which disappeared when the solvent was removed. There is no mention of symptoms from exposure to other substances. Because of the absence of this information, Gyntelberg's report does not comply with the definition of MCS.

The authors also mention that Stockholm and Cohr (1979) found that persons who had previously experienced solvent poisoning were more sensitive to solvents than other research subjects, during climate chamber experiments.

Rasmussen (2002) has confirmed that persons with nervous system damages, ***e.g.***, toxic encephalopathy, have enhanced sensitivity to organic solvents and often also to non-neurotoxic chemicals.

Occupational physicians in Sweden have had similar experiences (***e.g.***, Ørbæk, 1998; Lindelöf and Georgellis 1999, 2000) and Levy (1997) in Norway mentions that the second phase of MCS is often triggered after a long period of interruption of work and exposure. When these persons return to work, they can no longer endure exposure to chemicals, which they were previously used to. Nor can they endure them in lower concentrations. They begin to complain of diffuse symptoms when exposed to perfumes, exhaust gasses and the like. The same persons can also experience lowered tolerance towards alcohol and medicine.

An MCS-like syndrome was described in an occupational medicine investigation in France "***Syndrome d'intolérance aux odeurs chimiques***" (intolerance syndrome for chemical odours). In 19 out of 30 cases the symptoms were caused exclusively by exposure to organic solvents, corresponding to Gyntelberg's description (Grimmer, 1995). A sub-group of 17 out of the 30 later developed intolerance towards other substances. This phenomenon was called "***hypersensibilité olfactive***" (odour hypersensitivity). Not all of the 17 had previously been exposed to solvents.

A group from the Division of Environmental Medicine in Stockholm found that housepainters more than any other occupational group, suffered from MCS-like symptoms. In a questionnaire survey among active painters, 191 out of 584 respondents complained of odour sensitivity towards organic solvents, while 49 had symptoms fulfilling the criteria of MCS. The latter group of painters were clearly more bothered by their symptoms than the remainder (Lindeløf, 2000) (See also section 6.4).

Cones (1987) and Lax (1995) both describe a small group of persons with MCS among their occupational medicine patient groups consisting of 1200 and 605 referred patients respectively. 13 of Cone's and 35 of Lax's patients fulfilled Cullen's criteria. Most of Cone's patients had been exposed to organic solvents in the initial phase.

Table 4.1 Overview of MCS cases involving exposure to solvents (occupational medicine investigation)

Author	Syndrome	Number of Persons	Exposure	
			initial	"trigger" phase
Gyntelberg, 1986	Acquired intolerance to solvents	50	50 organic solvents	Organic solvents
Grimmer, 1994	Chemical odour intolerance syndrome ---------- Olfactory hypersensitivity	30 ---------- 17	19 organic solvents	Organic solvents And a "wide range" of other chemicals
Lindelöf, 2000	Odour sensitivity ---------- MCS	191 ---------- 49	Organic solvents ---------- Organic solvents	Organic solvents ---------- "a wide range"
Cone, 1987	MCS	13	11 organic solvents	"a wide range"
Lax, 1995	MCS	35	Not indicated	"a wide range"

4.1.1 MCS in workers after acute exposure to gasoline fumes during tunnel construction work

Davidoff (1998) tells of 77 unskilled construction workers who were exposed to chemical fumes from earth polluted by gasoline from a service station, during a period of two months when they were digging a tunnel. Not before two months after having noticed the smell of gasoline for the first time, did the workers start complaining of headaches, dizziness, irritation of eyes and throat, and coughing. Benzene concentrations of 60 ppm were measured in the tunnel air (Dräger tubes). The work was then stopped and the tunnel closed. More reliable measurements of all chemical fumes in the tunnel were not performed.

30 randomly chosen persons were examined twice: shortly after the episode and 10-13 months later, when 10 workers had developed symptoms fulfilling the MCS criteria. Two of these had previously been subjected to chemical fumes, while the other eight had not experienced symptoms prior to the tunnel episode (26,7% of the 30 tunnel workers examined).

The tunnel workers experienced symptoms less frequently (at least once a week) and for shorter periods of time than another group of MCS patients. But the symptoms were similar and from several organs such as the central nervous system, the respiratory tract, muscles, ligaments and joints, and the gastrointestinal tract.

The symptoms had not forced any of the workers to resign their jobs. Most of them were still working, when they were examined the second time.

This cohort of workers is rather unusual in an MCS context, since none of them knew anything about MCS, when they experienced their first symptoms. They have not been examined by clinical ecologists or had contact with the patient association for MCS victims, since then.

The investigation is interesting because it involves an almost experiment-like exposure situation where only some of the persons, who had previously been exposed and had been acutely poisoned, developed MCS.

4.1.2 MCS after exposure to plastics

50-75 workers at an airplane factory in the US became acutely ill, when a new plastic product was introduced. The symptoms resembled the ones known from acute solvent poisoning. The product was found to contain phenol, formaldehyde, and methylethylketone, which were measured inside the factory in concentrations below the limit value. Twelve workers complained of persistent symptoms due to various odours experienced in the everyday environment. A panel of experts examined them and found no other illnesses to explain their symptoms (Simon, 1990).

4.2 MCS after exposure to pesticides

According to Ashford and Miller (1998), exposures to organophosphate and carbamate pesticides have been emphasized as possible causes of MCS in several investigations. The course of events is typically an acute poisoning, sometimes accompanied by chronic symptoms of poisoning from the central nervous system and later development of diffuse symptoms from several organs, corresponding to the definition of MCS.

According to the patient association for MCS victims in the US, 80% of the 6800 members have stated that they know when, how and due to which substances they became ill. 60% became ill initially after exposure to pesticides (Ashford & Miller, 1998).

Tabbershaw (1966) reported on 114 farmhands in California with acute organo-phosphate poisoning. Some of these later developed an MCS-like condition. Three years after having been poisoned, 22 persons complained of indisposition when in contact with pesticides and organic solvents. Six persons quit their job due to symptoms. The others tried to avoid pesticides in

their work. 61 persons from the original cohort could not be traced and it is uncertain how many of these had moved away from the area due to MCS.

Cone (1992) describes an episode where 250 guests at a hotel were exposed to propoxur, a carbamate insecticide used against cockroaches, on several occasions. Many guests had momentary acute symptoms of poisoning, while 19 complained of persistent symptoms. They were examined at a clinic for occupational medicine some 5 to 15 months after the episode. Twelve of them complained of hypersensitivity to odours from perfumes, gasoline, printing ink in newspapers, various detergents, pesticides, and solvent-based products, which had not bothered them before the stay at the hotel.

Pesticide poisonings in eight countries (DK, S, N, UK, D, B, NL, GR), most of which occurred in working environments, are described in the EU report (1994).

Eight out of 23 persons in Germany with acute pyrethroide poisoning later developed MCS symptoms corresponding to Cullen's criteria. Clinical examinations and laboratory tests of these persons were normal (European report, 1994).

4.2.1 The situation in Denmark

Several cases of acute pesticide poisoning in gardeners and others have been reported from Denmark (Lander, 2000). No systematic investigations to show whether or not the victims fulfil the MCS criteria have been performed. According to Lander, a small group is bothered by odours, when they spray in the greenhouses. The cause of symptoms is ascribed to aromatic warning substances, which have been added to the pesticide (Lander, pers. Com., 2001).

As opposed to the situation in the US, where pesticides are the most frequently mentioned group of chemicals in connection with MCS, Danes do not use pesticides privately very often, and then mostly out-of-doors.

4.3 Wood preservatives – pentachlorophenol (PCP) in Germany

In connection with the European investigation, German experts reported on many cases of an MCS-like syndrome, primarily due to pentachlorophenol. This chemical was used on wood indoors and contained a complex mixture of substances such as dioxin, furan and organic solvents. 10,000 cases of poisoning (acute and chronic) have been reported. 100 of these were from children's institutions and schools.

The course of some of the cases fulfils the MCS definition with initial exposure to a substance followed by various non-specific complaints after exposure to quite low concentrations of various chemicals. A court in Frankfurt found it very probable that pentachlorophenol caused the MCS

complaints in a group of people. The manufacturer appealed the court decision but the outcome of the appeal case is not known (European report, 1994).

There are similar reports from other countries. High indoor concentrations of pentachlorophenol were measured in three towns in The Netherlands, where inhabitants complained of symptoms. But a connection between the symptoms and the substance could not be documented (European report, 1994).

In Belgium, the term ***PCP-Syndrome*** was used to describe a condition caused by the use of pentachlorophenol. Experts found many people with symptoms corresponding to MCS. They were interpreted as a form of intolerance rather than classical poisoning (European report, 1994).

4.3.1 MCS after exposure to Rentolin in Denmark

Rentolin is a wood preservative, which has been used indoors, by mistake. This product is only meant for use out-of-doors. But the importer advertised that it could be used for ceilings, floors and kitchen tables.

The product consists primarily of solvents (white spirit), linseed oils, and a fungicide (dichlofluanid).

For a period, many private individuals who had used Rentolin in their homes issued complaints. Several of these persons had been examined in occupational medicine clinics, where a pathological picture resembling MCS, with symptoms from the central nervous system and several other organs, was disclosed. Many of the cases were diagnosed as cases of acute poisoning by solvents, whereas the occupational medicine physicians could not document a connection between the use of Rentolin for the preservation of wood and the chronic MCS symptoms (Viskum, 1999). A toxicological assessment does, however, make a connection likely, especially if Rentolin is used extensively.

Subsequently, the Danish EPA has forbidden the use of Rentolin indoors, due to its high content of dangerous solvents.

Based on assessments by two experts on environmental medicine and indoor climate, a Danish court has ruled that Rentolin could be the direct cause of the MCS symptoms of the plaintiff. The experts were of the opinion that the dichlofluanid content, could have been of decisive importance.

4.4 MCS in relation to indoor climate

As mentioned in chapter 2, symptoms due to indoor climate can have many causes, which do not necessarily have anything in common with MCS. This section focuses on chemicals that can cause MCS-like symptoms.

These chemicals, which can be traced in indoor air and originate from various indoor sources, can collectively be termed volatile organic compounds (VOC). Wolkoff (1995) distinguishes between the following main sources:

- Construction materials, paint, glue, wallpaper, furniture, carpets, ***etc***.
- Materials from human activities: office machines, household machines, personal care, ***etc***.
- Micro-organisms: mould fungi, ***etc***.
- Out-of-doors air pollution from traffic and industry (see also section 4.8).

US literature contains many accounts from persons with MCS, whose symptoms started when they got a new office, moved into a new house, or had a new carpet laid. In most cases these persons worked in large office spaces with many employees , where 2-300 square meters of new carpet were laid. The carpet was glued to the floor with glue containing styrene and butadiene, which was put on the polymerised undersides of the carpet (Ashford & Miller, 1998).

Many more chemicals are used in private homes in the US than in Europe. For large parts of the population this can lead to greater indoor exposure to chemicals than in Denmark/Europe.

4.5 The Gulf War Syndrome (GWS)

In connection with previous wars (Vietnam, Korea), a limited number of soldiers were troubled by symptoms, some of which resembled MCS, after returning home. While these cases were previously assessed as being related chiefly to psychogenic traumas, other hypotheses are now being tested.

The large group of soldiers with health complaints after the Gulf War have led to large clinical investigations in the US and Great Britain. Several research projects are still running.

One of the many hypotheses for the cause of GWS is exposure to various chemicals (pesticides, vaccines, antibodies against poisonous gases, ***etc***.), which the soldiers were exposed to through inhalation or by injection. Some of the veterans with GWS may possibly fulfil the criteria for MCS, which means that they were exposed to an initial chemical poisoning by inhalation and since then developed various symptoms, when coming into contact with odours (see also remarks in section 2.3).

The Danish Gulf War Study did not disclose any exposures to chemicals before and during the Gulf War (Ishoy, 1999).

4.6 Comments

Due to a general lack of awareness of and interest in MCS in Europe and especially in Denmark not all of the variants of MCS-like cases, which might have occurred, are known.

By far, most of the cases are known from occupational medicine investigations, and they mostly have to do with exposure to solvents or pesticides. Two younger persons with MCS were employed in Danish public swimming baths. Chlorine fumes, which are formed under special circumstances, caused these symptoms (***e.g.***, trihalomethanes and chloramines). Both had to leave their job and be re-educated (Raffn, pers. com., 2001).

Graveling wonders why he finds that the people who work the most with chemicals and, therefore, should be the ones being exposed the most, have MCS less often. This remark does not correspond to the experience in Denmark, where most of the assumed MCS cases are linked to occupations where people have previously been exposed to solvents, and a few other occupations such as gardening and hairdressing, ***etc***.

Graveling does not mention his experience with, ***e.g.***, occupationally exposed cases. It is remarkable that Graveling and his co-authors, all of which are employed at an institute for occupational medicine, do not give figures for occupation-related MCS cases in Scotland and England. After all, the British Health and Safety Executive (HSE) commissioned their report (Graveling, 1999)(see chapter 3).

The cases involving the wood preservative Rentolin, which were mentioned above, are good examples of the few sporadic cases known from private homes.

4.7 Chemicals which can cause MCS

4.7.1 Chemicals and initial exposure in connection with MCS

The following chemicals have been mentioned in connection with MCS and initial exposure: All types of organic solvents (occupational or private), pesticides (organophosphates and carbamates), hair-care products (hairdressers) and substances containing chlorine (***e.g.*** public swimming baths).

Table 4.2 from the EU report lists statements of experts from the different countries regarding chemicals that are presumed to cause MCS. Organic solvents and pesticides are most frequently mentioned.

The basis for the Danish experts reporting that stress and psychosocial factors can elicit MCS (table 4.2 bottom) is unclear. These factors are not among the most well-known factors of initial exposure (see also subsection 2.2.2).

Table 4.2 Possible factors to elicit MCS (initial exposure). Information from nine countries in a European investigation (European report, 1994)

Exposure factor	DK	S	N	SF	D	NL	B	UK	GR
Amalgam / Mercury		+	+		+				
Anaesthesia gasses									+
Carpets and glue		+				+			
Diesel exhaust	+								
Formaldehyde	+		+		+				+
Hair-care chemicals	+	+							+
Indoor climate	+	+		+					
Degreasing agents	+								
Methylmethacrylate		+	+						
New, renovated buildings		+	+		+				
Organic solvents	+	+	+	+	+	+	+	+	+
Paint, lacquers	+	+			+				+
Pentachlorophenol, ***etc***.					+	+	+		
Pesticides	+		+		+		+	+	+
Drugs			+						+
Printing materials	+	+							
Stress – psychosocial factors	+	+			+			+	

4.7.2 Chemicals which cause multiple reactions (trigger substances)

Table 4.3 lists a wide, up-to-date variety of chemicals according to newer Danish information and literature from the US. The chemicals listed can be found indoors as well as out-of-doors at work, in public places, and in private homes.

"Indoor VOC, others" covers chemical fumes found nowhere else in the table. Wolkoff (1955) gives a detailed description of both the different causes of VOC and the large number of detectable organic substances (see also section 4.4). The range of VOC smell/odour concentrations includes many orders of magnitude (from mg/m³ to µg/m³ or even lower).

A number of exposures contribute to a complex type of air pollution involving combined effects from several chemicals and from chemicals and other factors.

Table 4.3 List of the most frequently reported triggering chemicals (*i.e.*, Miller, 2001)

Pesticides • Organophosphates, carbamates Organic solvents • Paint, lacquers, varnish • Glue • Metal cleaning • Printing ink and cleansing • Household chemicals • Nail polish remover Wood preservatives Formaldehyde Dry cleaning	Tobacco smoke Frying odour Chlorine fumes (public swimming baths) Asphalt Hair-care products (Ammonium compound) Automobile exhaust gasses Fumes from newly laid carpets Perfume, eau de cologne "Fresh-air" spray Scents in soap, washing powder and other household products Gasoline fumes Indoor VOC, others

Reactive substances can react with other substances and in this way create new compounds with triggering capacity. ***E.g.***, ozone reacts with citrus oil, creating a compound with a strongly irritating odour. By adsorbing to, ***e.g.***, dust particles, poorly evaporating chemicals can trigger via dust exposure (Wolkoff, 1999).

5 Frequency

5.1 Prevalence

When an illness to be investigated is not finally defined, it is difficult to find comparable epidemiological results. This is because the different research groups trying to describe the frequency of an illness find it difficult to adhere to common rules for defining illnesses, reporting, classification, selection ***etc***.

Mooser (1987) presumed the prevalence of MCS among people in the US to be 2-10%. He included people with MCS, who were forced to rearrange their daily lives as a result of their symptoms. Many experts, including Cullen (1994), regarded these figures as much too high.

The group behind the Interagency Report has only found three investigations with figures on prevalence published up to 1997. Two additional investigations have been made since then. These have all put standardized questions over the phone, to persons chosen randomly among a previously defined group of people or people from a geographical region. All investigations were made in the US.

Prevalence by objective diagnosis:

The people interviewed were asked whether a general practitioner had diagnosed MCS. The positive answers show the following frequencies:

- 0.2 % college students (Bell, 1993a)
- 4 % pensioners (Bell, 1993b)

• 4	%	pensioners	(Baldwin, 1997)
• 6.3	%	general public	(Kreutzer, public investigation of California, 1999)
• 1.9	%	general public	(Voorhees, 1998)

Subjective experience ("***self reported disease"***) of the people interviewed have produced more material on the prevalence of MCS.

Prevalence by <u>subjective</u> diagnosis:

Questions of whether exposure to several of the substances fresh paint, pesticides, perfumes, automobile exhausts gasses, and new carpets gave moderate or strong health complaints (needed to see a doctor, took medicine, was reported ill) gave the following frequencies of positive answers:

	4-5 substances	3-5 substances	2 substances	
students	15 %	22 %		(Bell, 1993 a)
pensioners	17 %			(Bell, 1993 b)
public employees		22.7 %		(Baldwin, 1997)
general public		33 %		(Meggs, 1996)
soldiers (+ Gulf War)			5.4%	(Black, 2000)
soldiers (- Gulf War)			2.6%	(Black, 2000)

Bell comments that their figures depend directly on how the questions about "having health complaints or feeling ill" were formulated. Based on a more detailed list including, ***e.g.***, new carpet, fresh printing ink, disinfectant, paint, natural gas, perfume, tar, pesticide, automobile exhaust, and tobacco smoke, the same group of researchers also investigated whether the students had symptoms due to one or more "environmental odours". Almost 10% had symptoms sometimes or often, while 28% had symptoms due to very few of the factors listed.

Baldwin's (1977) investigation covers symptoms due to out-of-doors as well as indoor air pollution among public employees working in modern well-insulated buildings.

Meggs interviewed randomly selected adults (general public) living in the rural areas. Among 51%, three groups of equal size had only allergy, only MCS, or both allergy and MCS. 3-5 of the substances in the list above produced symptoms in 33% of the two latter groups. Only 49% had neither allergy nor MCS symptoms. The authors were surprised at the high frequency, since they had expected a lower frequency of MCS in the rural areas than in the city.

Black's investigation by phone interview included 3700 soldiers divided into two groups, those who had taken part in the Gulf War and those who had not. The frequency of sensitivity to at least two substances from the usual list of trigger substances described above was surprisingly low (2.6%), and similar to objectively diagnosed MCS (by physicians), in soldiers who had not participated in the Gulf War. Black mentions that only 0.2% of the soldiers in the latter group had been diagnosed as having MCS by the military physicians. This corresponds to Bell's frequencies of MCS diagnosed by physicians among college students.

5.1.1 Prevalence of MCS in occupational medicine publications

Kipen (1995) investigated complaints of MCS-like complaints from various groups of people referred for examination at a clinic of occupational medicine or a general practitioner. He asked whether exposure to one or more of 23 trigger substances had created discomfort or had forced the individual to leave the room, quit the job, ***etc***. The positive answers were distributed as follows:

4 % out of 436 persons referred to a routine check-up
15% out of 107 persons referred due to another work-related illness
20% out of 41 persons referred to a general practitioner
54% out of 43 persons referred due to occupational asthma or bronchial hyper-reactivity but not MCS
69% out of 39 persons referred due to possible MCS (fulfil Cullen's MCS criteria).

In this last group significantly more of the 23 substances chosen created symptoms than in the other groups. The group referred due to asthma delivered a similar, though less accentuated, result. Kipen did not investigate whether persons from the four control groups, who had given positive answers, had MCS or not.

The table below shows the prevalence of MCS or similar conditions among occupational medicine patient groups.

Table 5.1 Prevalence of MCS and odour sensitivity in occupational medicine materials (W = women)

Author	***Number of persons***	***Sex***	***Syndrome***	***Number of patients***	***%***
Gyntelberg	160	14% W	Intolerance towards organic solvents	20	12.5
Grimer	?	53% W	Odour sensitivity ---------- Odour hypersensitivity – MCS	30 17	- -
Lindelöf	584	<10% W	Odour sensitivity ---------- MCS	191 49	32.7 8.4
Lax	605	80% W	MCS	35	5.8
Cone	1200	70% W	MCS	13	1

The papers cited in the table above (also mentioned in chapter 4) give an interesting perspective of the prevalence of odour sensitivity and MCS respectively. While the two papers from the US (Lax and Cone) use the traditional MCS definition to identify possible MCS patients among a mixed occupational medicine clientele, the three groups from Denmark, France, and Sweden describe two stages of development of MCS.

The condition described by Gyntelberg possibly corresponds to odour sensitivity and can be regarded as an initial stage of MCS, while the groups in the French and Swedish material fulfil Cullen's MCS criteria.

The materials from the US and Europe are different regarding sex. This can be because comparatively more men in Europe can be exposed to organic solvents at work. Lindelöf's investigation of housepainters in Stockholm probably involves an effect of selection. But it is surprising that so many women appear in the American occupational medicine materials.

The European and American materials do not appear to be comparable.

It should be added that Lindelöf's housepainters are still working in spite of MCS. The other materials contain no information on the social situation of the people investigated.

5.2 Incidence

Most American investigations confirm only two common characteristics of MCS patients regarding the incidence of MCS, found in the literature (Cullen, 1992; Sparks, 1994):

1. Most patients are women.
2. They are more than 30 years old, when symptoms first appear.

Kreutzer (1999) included a large proportion of the people in California in his investigation. But he found no differences due to race, place of residence, education, or social situation among the positive answers.

Miller and Mitzel (1995) investigated the socio-economic aspects of MCS. In 83% out of 112 persons with MCS (Cullen's definition), the illness started when they were more than 30 years old. 81% of these were employed full time when the illness started, as opposed to 12% when they were interviewed. The symptoms have forced most of the group to take up other vocations. 40% have consulted more than 10 physicians for help.

5.3 Prevalence according to clinical ecologists and patient organisations

Descriptions based on the experiences of clinical ecologists and MCS patient organizations in the US contain much information on the frequency of MCS. Spyker (1995) from an ecological environmental clinic in the US finds that the average age of MCS patients is 40 years and that 77% of them are women. Rea (1992), whose 4-volume publication "Chemical sensitivity" describes his experiences through 20 years with more than 30,000 patients with environmental illnesses, corroborates these figures. Not all patients have been diagnosed with MCS. The incidence is based on definitions of illness and symptoms, which cannot be compared with other literature and, therefore, can hardly can be used in the context of this report.

5.3.1 Frequency of MCS in Denmark according to patient organisation

The Danish MCS Organisation estimates that 4% (200,000) of the population in Denmark has MCS. This figure is based on frequencies from the US. The organisation says that many cases of headache at work could be symptoms of non-recognized MCS due to exposure to chemicals.

5.4 Comments

There is some epidemiological documentation for the existence of MCS in the US, Canada and Europe. The frequency is about 0.2-6% in the US.

No certain data exist for Europe. In both Sweden[1] and Germany[2] nationwide investigations of the frequency of MCS were completed in 2001. The data had not been published, when this report was finalized (see also Annex H).

Danish occupational physicians estimate the prevalence of MCS in the Danish population as a whole to be 0.1-1%. The higher prevalence figures, shown for the US compared to Denmark, can have many causes. One could be that Americans are more often exposed to chemicals, and not least indoors. Another could be that there are comparatively more clinical ecologists with knowledge of MCS, who diagnose and treat MCS patients in the US, whereas in Scandinavia, at least, it is mostly specialists in occupational and environmental medicine (to whom the MCS diagnosis is more controversial), who get these patients.

In the US, MCS is mostly an indoor illness in women of about 40 years of age.

The prevalence of MCS in occupational medicine patient groups in the US and Denmark is about equal, 1-12 %. These figures apply to a limited group with greater risk of acquiring MCS than people in general.

In connection with a possible strengthening of MCS research in European, one of the most important tasks will be to get more reliable figures on the prevalence of MCS.

Table 5.2 Prevalence of MCS in Denmark and the US

	Denmark	The US
Prevalence in the entire population	≤ 1% (estimated)	0.2 – 6%
Exposure	At work	In the home
Sex	?	Women
Age	?	> 40 years

[1] ***Institute of Environmental Medicine***, Karolinska Instituttet, Stockholm, Sweden

[2] ***Umweltbundesamt*** and ***Robert Koch Institute,*** Berlin, Germany

6 Possible causes and mechanisms of illness

Research into the illness mechanisms behind MCS concentrates on four main categories, three physiological ones and a psychological one:

1. Immunological mechanisms,
2. mechanisms in the mucous membrane of the nose,
3. neurological mechanisms, and
4. psychological mechanisms.

Another hypothesis is based on a new illness concept:

5. Toxic-induced loss of tolerance (TILT),

and, finally, the

6. illness model of clinical ecology

proposed by the ***American Academy of Environmental Medicine (AAEM).***

All these mechanisms are still being discussed. The most important research results and arguments for pathogenesis are presented for each mechanism.

6.1 Immunological mechanisms

The immonological mechanism is the most cited physiological illness mechanism behind MCS. Clinical ecologists in the US are especially fond of this mechanism. Some, including Rea (1992), who works on the basis of the AAEM theory, have suggested that the cause of MCS is a chemically triggered disturbance of the immune system, which can influence other bodily functions. An example of this can be an interaction between the immunological and the neuro-endocrine systems (see section 6.3, neurological mechanisms) (Meggs, 1992; Levin, 1992). Others recognize similarities between immunological responses and inflammatory reactions and suggest, therefore, that an overlapping between the two mechanisms is responsible for MCS (Meggs, 1992).

These hypotheses have not been proven. Since the first years when MCS was described as a hypersensitivity illness, many have sought an MCS-typical immune response among the classic immune responses, in vain. Others have tried to detect an MCS-specific immunological biomarker. Rea (1992) and his colleagues from an eco-health centre, who have performed more than 5000 immunological tests, though not only for MCS patients, have published many results, which correlated well with MCS. They have discovered special subgroups of white blood cells, a special fraction of activated white blood cells, abnormal antibodies against the body's own cells, and new compounds consisting of chemicals bound to proteins. Other scientists have not been able to reproduce Rea's discoveries. This they attribute to differences in research methodologies and scientific demands concerning the blinding principle and reproducibility.

Thus, no clear pattern of impacts on the immune system has been shown to exist in connection with MCS, neither as an immunological weakening nor as a strengthening (Terr, 1986; Simon, 1993). Great differences with respect to methods and quality control in connection with the investigations is the most likely explanation of such a discrepancy between the results of Reas' group and of the others. When the demands on methods and quality have been strict, it has been impossible to discover any illness indicators among the immunological parameters.

Simon (1993) assessed the applicability of immunological tests as biomarkers in a carefully planned study of MCS patients and a control group (concerning biomarkers, see chapter 7). Laboratory tests were carried out in a special laboratory used by clinical ecologists. None of the tests used could identify persons with MCS. Double checks of the same blinded blood sample in this laboratory gave conflicting results (Simon 1993; Friedmann 1994).

Margolick and his associates have come to the same conclusion (Mitchell, 2001).

6.2 Mechanisms in the mucous membrane of the nose

Enhanced sensitivity to odours found in MCS patients has occasioned an investigation of this condition as a possible explanation of MCS.

The mucous membrane in the nose contains chemo-sensitive nerve fibres from two brain nerves: the olfactory nerve (***nervus olfactorius***) with nerve endings in the upper part of the nasal cavity, and the fifth brain nerve (***nervus trigeminus***) with nerve endings everywhere in the nasal cavity. Chemicals (odours) stimulate both nerves. Stimulation of the olfactory nerve fibres creates a sense of smell, while stimulation of nervus trigeminus creates a sense of irritation. The two brain nerves transport the impulses received along different paths to centres in the brain, creating different sensations.

Ørbæk (1998) performed provocation tests with odours and chemical irritants in high concentrations on people with toxic encephalopathy (TE) and on normal persons. As opposed to the normal persons, the persons with encephalopathy experienced the odours as extremely uncomfortable irritants. Before the tests, both groups were shown to have normal odour thresholds.

With a double-blind test, Hummel (1996) demonstrated that MCS patients have a non-specific over-reaction, expressing an altered pattern of reaction, when exposed to irritants.

Caccappolo (2000) and his associates tested the reactions of three patient groups 1) with MCS (Cullen's criteria), 2) with chronic fatigue syndrome, and 3) with asthma and some normal persons to chemicals, a pleasant odour and a disagreeable smell. All groups had the same odour threshold. But phenylethyl alcohol (pleasant odour) in concentrations above the odour threshold created a burning sensation and pain in MCS patients, whereas disagreeable smells did not create the same unpleasant sensations. The other groups did not react abnormally, although several persons with chronic fatigue syndrome showed the same reactions as the MCS group. The authors emphasize that the reactions of MCS patients to the odour test did not follow current neurophysiological mechanisms.

Another Swedish group has exposed housepainters with and without MCS to a scent substance with a pleasant odour (furfuryl mercaptan), to chemicals (acetone, VOC), and to combinations of these (Georgellis, 1999). The author did not expect the scent substance to create unpleasant reactions. The persons with MCS experienced the substance alone or in any combination as extremely unpleasant, whereas acetone and VOC by themselves were, by no means, unpleasant.

Meggs' group investigated hypotheses based on the possible role of special nerve fibres (C fibres) and inflammation of the mucous membranes of the

respiratory tract. They studied nose and throat in ten MCS patients, of which nine had complaints from the nose. Chronic-inflammation-induced changes were found in all of them (Meggs, 1993). Meggs suggested that it could be a ***Reactive Upper airway Syndrome (RUDS),*** analogous to the ***Reactive Airways Dysfunction syndrome*** (***RADS)***, an asthma-like condition, which develops from acute exposure to respiratory tract irritants.

Cain (2001) found that persons with recurrent inflammation of the mucous membrane of the nose had enhanced odour perceptibility when the membranes were inflamed, compared to when they were not. Bascom (1992) investigated the role of the mucous membrane of the nose in connection with the development of MCS, assuming that chemicals stimulate the C fibre-containing nerve cells, which are found everywhere in the mucous membrane of the respiratory tract. A stimulation of these fibres in laboratory animals caused substances (neuropeptids) to be released locally. These could cause contractions in the respiratory tract, increased production of mucus, dilation of blood vessels, and increased permeability.

Several other authors have based their hypotheses of the mechanisms behind MCS on inflammation of the C fibres of the nervous system. Substances (substance P) creating local inflammations, which can contribute to the development of MCS symptoms, are released from the nerve endings with C-fibres(Meggs, 1995).

Bascom (1992) described how chronic irritation of the surface of the mucous membrane creates inflammational changes in the nerve end. These changes lead to increased susceptibility to the chemical effects of various respiratory tract irritants. She maintains that a similar inflammatory reaction should be involved in other conditions such as migraine, headache, and to a lesser extent arthritis and fibromyalgia.

Two additional mechanisms in the mucous membrane are mentioned as possible contributory mechanisms. The first is the release of substances (interleukins), which influence the brain, from nerve cells. The other is a theory on "***neural switching***", a type of "switching between nerve paths", according to which a chemical stimulation of the mucous membrane of the nose creates a response from another organ, ***e.g.***, palpitation and headache (Meggs, 1995). As illustrations of ***"neural switching"***, Meggs mentions, ***i.e.***, respiratory tract symptoms and nettle rash (***urticaria***) from food allergy and mucous membrane reactions in eyes and nose from eating strong spices. Stimulation of nerve fibres of the trigeminus nerve in the nose and throat can create a protective reaction from the heart with reduced heart rate and pumping action (Ashford & Miller, 1998).

Referring to animal experiments, Sparks (1994) mentions that the release of a nerve substance (interleukin) in relation to nerve tissue inflammation might explain how symptoms are created in various organs in connection with MCS.

6.3 Neurological mechanisms

6.3.1 The olfactory-limbic system

Bell (1992) and his associates are behind most of the research having to do with the hypothesis on an interaction between the olfactory nerve, the limbic system (the brain centre controlling emotions and behaviour), and hypothalamus (the brain centre for the autonomous and endocrine control of organ functions). Our physiological, cognitive, and behavioural reactions are integrated through this system, which also governs the immune response and the hormonal and autonomous control systems. An impact on the limbic system can create changes in most of the bodily functions and in all organs, which corresponds to the symptoms of MCS.

Bell describes how chemicals can enter the nervous system via the olfactory nerve, which is directly connected to the brain. The so-called blood-brain barrier surrounding the brain is circumvented in this way. Experiments with rats show that a substance is transferred from the nerve fibres in the nose to the point of entry of the olfactory nerve into the brain (bulbus olfactorius) and further to other parts of the brain. This mechanism of transport has not been found in humans, but in rats that have inhaled high concentrations of manganese (Brenneman, 2000). This way of access would explain how a chemical reaches the limbic structures in the brain as a starting point for the sensitisation theory.

Neural sensitisation (sensitisation of nerve tissue)

The limbic system consists of several structures, including “amygdala”, “basal ganglia”, “septum” and “hippocampus”, all of which are located in the brainstem. Experiments on animals have shown that amygdala can be sensitised relatively easily (Antelman, 1994). Sensitisation in this context is when repeated exposures to the same substance create an increased response in the organism at concentrations that would normally not create any response at all. Neural sensitisation can be attained by both “kindling” and “non-kindling” mechanisms.

Kindling is an experimental method aimed at detecting a change in the reaction of the nervous system to external stimuli. Repeated chemical or electrical stimuli, in so low concentrations/doses that they do not provoke a reaction, can lower the threshold concentrations or doses creating cramps.

Non-kindling stimulation gradually increases the response of the animal to repeated chemical/non-chemical stimulations over time. Responses are neurochemical, immunological, hormonal or behavioural (Bell, 1997b).

Both mechanisms of neural sensitisation support a theoretical explanation of why patients with MCS complain of symptoms in several organs (Bell, 1995). According to Bell (1997a), the sensitisation mechanism differs from, ***e.g.***, the mechanism behind the conditioned reflex, the point of departure of which, is

also the limbic system. But she hints that both mechanisms may help explain the mechanism behind MCS.

Several research groups have confirmed the neural sensitisation mechanism through experiments with animals (Sorg, 1994; Sorg, 1995; Bell, 1997c). Gilbert observed changes in the electrical brain activity and epileptic-like fits in rats after prolonged exposure to Lindan (a pesticide) in low concentrations, whereas nothing happened, when the rats were given a single cumulative dose of Lindan (Gilbert, 1995). Other experiments with animals support the hypothesis that reactivity to, ***e.g.***, chemical stimulation can be partly genetically based. A special strain of rats ("***Flinders sensitive Line rats**")* with additional nerve receptors and greater sensibility to the organophosphate diisopropylenefluorinephosphate (a pesticide) than other strains, has developed behavioural changes similar to those of depressed humans (Overstreet, 1996).

An experimental investigation has shown that medicine, which should not be able to enter the brain because of the existence of the blood-brain barrier, did so none the less, when the experimental animals were stressed (Friedmann, 1996). This observation can support the neural sensitisation hypothesis. That the substance could enter the brain during stress illustrates the hypothesis that a traumatic experience can contribute to or trigger MCS.

Bell and associates found a connection between a highly developed sense of smell and functional disturbances of the limbic system. This was expressed by increased psychological problems such as substance abuse, anxiety and depression in a group of students with increased odour sensitivity (cacosmia) compared to students with a normal sense of smell (Bell, 1996a).

Other symptoms, such as memory problems and prolonged reaction times during neurophysiological testing compared to control groups, which may also have been triggered via the limbic system, have been seen in soldiers from the Gulf War and in other persons with chemical intolerance respectively (Bell, 1996b; Bell, 1997c).

One investigation has tested the neural sensitisation theory on two patient groups with MCS and asthma respectively and a control group, using neurophysiological methods. Bell's theory, according to which MCS patients should have greater cognitive problems than the other two patient groups, could not be corroborated (Brown-DeGagne, 1999).

6.3.2 Other mechanisms related to the neurogenic mechanism

Arnetz' integrated model for MCS

Arnetz proposes a model based on the neural sensitisation theory, and which is more suited for a rational and co-ordinated research effort.

This concept is based on the assumption that sensitisation of the limbic system creates a change in the pattern of reaction, which can be measured by objective criteria. Both physiological and psychogenic factors can bring about this sensitisation (Arnetz, 1999).

The first step in the course of events consists of an initial exposure, which can be ***reversible***, that is, the person being exposed recovers, or it can be ***irreversible***, which means that the limbic system is sensitised; the person is sensitised.

As opposed to Bell, who assumes that a chemical or chemicals penetrate the olfactory-limbic system, Arnetz also sees other types of first-step influences causing sensitisation of the limbic system. These can, ***e.g.***, be strong psychosocial stress or a "life trauma" (***e.g.***, so-called ***posttraumatic stress disorder)***.

The sensitised limbic system reacts to an enlarged selection of triggering influences – not chemicals and odours only, but also noise, electromagnetic fields, ***etc***.

Arnetz expects to be able to document enhanced limbic sensitivity and reactivity as changes in neurophysiological, neuroendocrine, and endocrine parameters.

Arnetz' theory has been used by Georgellis (1999) in investigations involving Swedish housepainters with and without MCS. Painters with MCS experienced a pleasant odour as a very uncomfortable odour and reacted with stress, anxiety and reduced coping ability compared to painters without MCS. The MCS group also had significantly more symptoms from skin and mucous membranes and they were more tired than the control group. This implies that the changes observed in painters with MCS were due to a reaction in the limbic system.

Uncertainty and fear of being harmed when provoked can, however, have been the main cause of stress.

6.3.3 Changes in the functioning of the brain

Electroencephalograms (EEGs) and all modern electronic methods of examining the functioning of the brain (***brain electrical activity mapping*** (BEAM), ***positron emission tomography*** (PET), ***single photon emission computed tomography*** (SPECT) have been used to investigate persons with MCS. Although several of the investigations mentioned have shown changes, Mayberg (1994) concludes that these changes are not the final proof, because all of the investigations were vitiated by methodological errors such as lack of standardization of the technical equipment, no control of reproducibility, and no use of control groups.

Heuser (1994) showed that the bloodflow through the brain of persons, who have been exposed to pesticides or organic solvents, has a different pattern than in persons, who have not experienced the same exposure, in depressed persons, and in persons with chronic fatigue syndrome. Unfortunately, the importance of the reported findings is weakened, since information on exposure and criteria for MCS is lacking. Lorig (1994) has shown that odours in low concentrations bring about changes in the electroencephalograms of normal people, which is an indirect objective indication of impact on the brain. Both of these investigations could be the first steps towards finding a biological indicator for MCS. Others should, therefore, look into them.

6.4 Psychological mechanisms

6.4.1 Conditioned reflexes (Pavlov's reflex)

As an analogy to the mechanism behind the classic Pavlov's reflex, somatic symptoms are created as a response to influences, which normally do not create such symptoms. Many are of the opinion that this mechanism is the main cause of MCS. This is especially obvious when the symptoms occur as a result of exposure to chemicals, ***e.g.,*** in connection with an accident (Siegel, 1997).

This corresponds to the situation in Denmark, where most MCS cases are reported from clinics of occupational medicine. Many Danish patients with chronic solvent poisoning have probably, to some degree, experienced their multiple episodes of poisoning as traumatic events.

The occupational physician Cullen (1992) does not consider MCS in people, who have been exposed to solvents, to be a conditioned reflex.

Traumatic childhood experiences (***e.g.***, physical and sexual abuse) are emphasized as triggering or facilitating factors. One investigation showed that 60% of patients with chemical sensitivity had such experiences in their childhood, and that psychotherapy reduced MCS symptoms. This created the hypothesis that odours experienced in connection with traumatic events can trigger the conditioned reflex (Staudenmayer, 1993). The investigation suffers from several weaknesses, ***e.g.***, unclear criteria for selecting patients, which weaken the conclusions. This hypothesis has not been investigated further.

Other studies show that many people with multiple organic symptoms were abused in their childhood, and that persons who have experienced violent assaults, complain of minor symptoms more often than those who have not (Pennebaker, 1994). That psychotherapy helps in such cases can be taken as indirect proof of the causal hypothesis (Staudenmayer, 1993).

With a method using conditioned reflexes, a Belgian research group was able to create and later eliminate odour-related symptoms in healthy persons (Van den Bergh, 1999). The author concludes that the mechanism behind MCS can be explained, at least in part, as a Pavlov reflex.

6.4.2 Psychogenic factors

It is clear that many persons suffering from MCS complain of anxiety and depression, and many consider this to indicate that MCS has psychogenic causes. Many have mentioned the “iatrogenic” model, where the physician or therapist induces the patients to develop and sustain their symptoms and conception of illness (Black, 1995).

A group of persons were exposed to odours and the intensities of these and the symptoms and discomforts experienced were recorded. Prior to exposure, all of the subjects received information on the odours. One group received negative information and the other received positive or neutral information. The first group felt that the odours were intensified and created discomfort and health complaints, , whereas the other group did not have the same experience (Dalton, 2000; Hummel, 1996).

Many investigations of groups of people with environmental illnesses have shown that among these, more often than among others, are people predisposed for personality disturbances, depression and anxiety symptoms, and somatic and hypochondriac symptoms - all of which indicate that these people may have hidden emotional problems (Black, 1993). On the other hand, people with increased odour sensitivity (cacosmia) have been shown to be more susceptible to feeling anxiety or becoming depressed (Ashford & Miller, 1998).

Personality factors can have to do with the mechanism behind MCS. Women are quicker to develop physical symptoms in stressful surroundings than men. People with chronic anxiety experience all forms of pressure negatively, creating discomfort and health complaints.

These factors are also mentioned in connection with other illnesses, including environmental illnesses. These factors may be of importance as psychosomatic factors behind the pathogenesis of MCS.

Leznoff (2000) observed typical signs of fear reaction accompanied by hyperventilation when MCS patients were exposed to triggering substances. He makes reference to the fact that several triggering symptoms in connection with MCS can be explained by a physiological reaction in the blood circulation of the brain during hyperventilation.

7 out of 13 patients with environmental illnesses had experienced anxiety and depression before they became ill (Simon, 1990). In 38 out of 90 persons filing for compensation for an occupation-induced environmental illness (62 of these with multiple symptoms), psychiatric diagnoses such as depression, anxiety, stress, and psychosomatic symptoms were found. Several had more than one diagnosis. But none of these persons had a psychiatric diagnosis, before they acquired the environmental illness (Terr, 1989). The number and distribution of the psychiatric diagnoses were not reported.

Fiedler (1996) investigated the frequencies of psychiatric diagnoses among her patients on several occasions. In an investigation involving 36 persons with MCS or chemical sensitivity (CS) and 18 controls, several of the 36 had or had had a psychiatric illness. But more than half of the 36 had never had a psychiatric diagnosis. 96 persons with MCS, CS or chronic fatigue syndrome (CFS) and a control group were subjected to neurophysiological and standardized psychiatric tests. More abnormal test results indicating psychiatric illnesses were found in the three groups with MCS, CS, and CFS than in the control group. But 74% of the MCS patients, 38% of those with CS, and 61% of the ones with CFS had normal test results.

Out of ten investigations of the importance of psychogenic problems in connection with the emergence of MCS, considerable methodological problems were discovered in the nine, including the mixing of cause and causal relations in eight cross-sectional investigations (Davidoff, 1994). In a more recent investigation where 1166 persons were tested for MCS, Kutsogiannis and Davidoff (2001) found that psychological factors were not over-represented in persons fulfilling the MCS criteria, compared to the others.

6.4.3 Environmental somatization syndrome

The somatization syndrome, which is often cited in connection with environmental illnesses, including MCS, is based on a psychosomatic mechanism. The pattern of reaction is connected to a tendency in us all to connect illness with an outside agent, while many of us are also latently disposed to developing somatic symptoms in one form or another (headache, fatigue, insomnia, muscular pains (myalgia), ***etc.***) when we are exposed to stress, have personal problems, or are anxious or depressive. The international name for this pattern of reaction is ***individual determined response (IDR)***.[3]

In a chapter of a recently published textbook on environmental and occupational medicine, Rasmussen and Hildebrandt-Eriksen (2001) describe the Danish experience with odour hypersensitivity, which is grouped together with other environmentally determined somatization disorders. The authors consider the illness to be determined by an interaction between the personality structure of the patient and factors in the patient's physical and social environment. They also regard a conditioned reflex like the Pavlov reflex as a possible contributing factor in case of acute overexposure to irritating substances**.** The authors also mention, that " … persons with injuries to the nervous system, ***e.g.***, toxic encephalopathy, experience enhanced sensitivity to organic solvents and also to non-neurotoxic chemicals in general. We are presumably dealing with other mechanisms than in otherwise healthy persons."

Thus, the authors group odour hypersensitivity together with somatization disorders, while they suspect another illness mechanism to be behind MCS, when it occurs in persons with symptoms from exposure to solvents. The assumed illness mechanism associated with the latter patient group is not elaborated upon.

6.5 Toxic-induced loss of tolerance (TILT)

The hypothesis associated with TILT, developed by Miller (1997), chooses an induced weakness or the elimination of natural tolerance towards external stimuli (***e.g.***, weakening of the defence mechanisms of certain organs, similar to the reduced tolerance to sugar of diabetics), where a response is triggered at very low concentrations, as a starting point.

This theory is based on a new concept of illness involving weakening or loss of tolerance. Miller also considers this mechanism to be the cause of other illnesses such as migraine. The definition of change in tolerance is the opposite of the change in tolerance connected to drug misuse, since TILT is associated with increasingly ***lower*** concentrations of the trigger substance(s) inducing the response. The mechanism behind the loss of tolerance is based on neural sensitisation.

TILT as a cause of MCS, proceeds in two phases: an initial phase involves exposure to chemicals (preferably pesticides, organic solvents or indoor VOC). Not all people exposed develop loss of tolerance. Some do not develop permanent symptoms following the first exposure and recover. Other more susceptible persons develop weakening/loss of tolerance.

During phase two involving exposure to the same or other chemicals or substances in very low concentrations, various organs react with a so-called "trigger response". Different substances create different responses (***e.g.***, diesel fumes create headaches, food odours lower the ability to concentrate, perfumes creates nausea, ***etc.***). Several daily exposures can create overlapping symptoms from several organs, making it impossible to find the connection between symptom and trigger substance (***masking***). Exposure to several trigger substances over a number of days can perpetuate the symptoms. This state of affairs can be upheld by constant exposures to new trigger substances (***habituation***).

Miller sets the diagnosis by testing in a provocation chamber taking both ***masking*** and ***habituation*** into account. The patient must be free from trigger substances, before the provocation test is performed.

6.6 Illness model based on clinical ecology

This model uses concepts and definitions, which most physicians and researchers are unfamiliar with and usually do not use in connection with their research. The clinical ecologists consider this model and its concepts to offer a better understanding of the pathogenesis behind MCS, as well as other environmental illnesses (Rea, 1992).

According to the ***holistically oriented illness model for environmental illnesses***, to which MCS belongs, many illnesses of hypersensitive people are based on a malfunctioning of one or more of the biological systems of the body: As part of a defence reaction against "environmental stressors", described as a form

of detoxification, an unbalance is created in the bodily homeostasis, followed by a reaction from the bodily organs. The mechanism of unbalance can be caused by defective enzyme systems or vitamin, trace element, ***etc***. deficiency. Reactions from organs create symptoms. The defence mechanism has several aspects and is based on individual susceptibility, pattern of response and adaptation (AAEM, 1992) (see also definition of environmental illness in Annex A).

The following concepts are used to describe the model further:

Total load	The sum of all external environmental "stressors", which a given person is exposed to at a given time
Adaptation	The human body attempts to maintain homeostasis.
Mal-adaptation	The biological mechanisms of the body are overtaxed, perhaps weakened by acquired/genetic factors, and cannot maintain homeostasis: illness results.
De-adaptation	Mal-adaptation recedes to adaptation when the body can neutralise/eliminate the substance(s), which caused the over-taxation.
Bipolar response	Dynamic, two-phased response of the body expressed as stimulation – non-stimulation caused by external environmental factors, explains why varying patterns of response can be seen in environmental syndromes.
Spreading phenomenon	Acute – chronic development of sensitivity to substances that have not previously caused acute symptoms – chronic development of sensitivity in new organs, which have not reacted before (see mal-adaptation).
Transfer phenomenon	Symptoms jump from one organ to another.
Individual sensitivity	Among a group of persons, who are sensitive to a substance, each will react and express symptoms in their own special way. The same symptoms shown by a group of persons have different causes (each has a personal "list" of substances, to which they are hypersensitive)
Incitant	Trigger substance or cause of symptoms in connection with both allergy and non-specific hypersensitivity
Environmental stressor	Each substance or situation which can destabilise the homeostasis of a sensitive person.
Homeostasis	All bodily functions are in mutual balance.

All descriptions of investigations and research by the clinical ecologists are based on the principles listed above. The illnesses are documented by measurements of very specific organ and enzymatic functions and metabolic

processes (***e.g.***, glutathion metabolism), and by the lack of various trace elements. Accurate standard values for such measurements do not exist in general clinical medicine.

Dr. Kuklinski (2001), director of Ambulanz in Rostock (Centre for diagnosis and treatment of environment medical illnesses) is of the opinion that most physicians lack knowledge about the facts mentioned above and, therefore, are unable to diagnose illnesses like MCS.

It is surprising that the holistic illness model does not include the possibility of psychological factors being involved in the pathogenesis of the illness.

6.7 Discussion

The problem concerning the causal relationship between MCS and the mechanisms behind it resemble the well-known "***black-box***" situation. It is possible to describe:

A. What a person was exposed to initially and

B. what the symptoms are, when a person has MCS.

But what happens between A and B is not known: What mechanisms make a person develop the symptoms when exposed to a chemical, which he/she had no problems with before?

It seems that the course of events having to do with MCS proceeds in ***two phases***. First there is the ***exposure phase***, which for most of the exposed persons has no permanent effect (they do not become sensitive to chemicals). Then there is the ***trigger phase***, where a few of the persons who were exposed initially, get symptoms when exposed to low concentrations of trigger substances. A few of the people afflicted can recover.

Conditions of exposure

Many researchers refer to the course of events described above, but no investigations segregate clearly between the two phases of development of possible illness mechanisms. This is remarkable, since what happens in the initial phase seems very different from what happens in the trigger phase. Certain persons develop a chemical intolerance in the initial phase. This can happen when exposed to high concentrations of a chemical or during a serious virus infection (***e.g.,*** mumps in adults) or through psychogenic shock or trauma. No research results describe mechanisms leading to chemical intolerance or discuss the significance of infection or shock/trauma.

During the trigger phase very low concentrations of chemicals create symptoms. The research reports dealt with in this chapter deal with mechanisms of the trigger phase.

According to Bell's theory, the effect created by initial exposure (chemical intolerance) can also be created by repeated exposures to smaller doses over a longer period of time. This hypothesis seems to be based on a combination of phenomena of the initial phase and of the trigger phase. Many researchers include a similar concept in their hypotheses for illness mechanisms behind MCS.

Mechanisms

One of the most plausible hypotheses for the MCS syndrome is: A complex reaction from main brain centres of the limbic system. Various mechanisms may be able to explain, how low concentrations of a chemical create this reaction in the brain.

An **immunological mechanism** is possible, but a comprehensive pattern of change is lacking, both among the individuals and in each individual.

A **mechanism based on the mucous membrane of the nose** and the odour-sensitive nerve fibres also seems likely. Several research results point at a reaction of the brain to nervous impulses from the olfactory sense or a mechanism based on the release of biologically active substances from nerve cells in the mucous membrane of the nose.

The theory on neural sensitisation in the olfactory-limbic system offers a plausible explanation of MCS – a chemical in small doses can, over an extended period of time, cause an increased and changed response from the limbic system of the brain. Bell's model on "limbic kindling" fits the description of MCS and corresponds to the neurophysiological functioning of the brain.

Finally, MCS may be based on a toxic mechanism. The literature on organic solvents includes descriptions of the limbic system of the brain being affected in persons with toxic encephalopathy, and a toxic mechanism is assumed to be involved. This chapter presents results from many research reports describing MCS or MCS-like conditions in persons who have been exposed to toxic doses of organic solvents.

It is difficult to prove or disprove that MCS in some persons has psychogenic causes or is due to a psychiatric ailment and, conversely, that MCS is the cause of psychogenic symptoms. Existing psychogenic problems can contribute to MCS. That psychological problems can increase the susceptibility of some persons to environmental impacts is well documented (individual increased susceptibility). This psychological factor plays a role during initial exposure as well as in the "trigger" phase of MCS patients.

This hypothesis entails, ***e.g.***, that persons predisposed to fear and depressions are in greater risk than others of acquiring MCS when exposed to chemicals.

A large group of MCS researchers agree that psychological mechanisms can sometimes trigger MCS, but most probably not in all cases. A connection exists between MCS and psychological factors, but this is not to say that there is a direct causal connection between the two (Graveling, 1999).

The conditioned reflex, especially the character and pattern of the response, does not correspond to an MCS response (***e.g.***, the tunnel workers mentioned in subsection 4.1.1). It can be debated whether the mechanism behind the odour hypersensitivity of Danes having been exposed to solvents is due to a conditioned reflex. If so, then the exposure itself has been a traumatic experience.

This possibility exists and several Danish occupational physicians support this mechanism as an explanation of odour hypersensitivity. But no Danish investigations support this supposition. Ørbæk's (1998) investigation of two persons with toxic encephalopathy points to other mechanisms. Van den Bergh et al. (1999) consider the mechanism of MCS to be a conditioned reflex, but it is hardly the primary mechanism behind all cases of MCS.

Most people can accept a mixture of a psychogenic and a physical illness mechanism to be behind an illness. At present, several researchers refer to interactions between psychological, physiological and other (social) factors as mechanisms behind MCS.

Based on this hypothesis it is assumed that the pattern of symptoms connected to MCS is created by a physiological-psychological impact on the olfactory system and other brain centres (amygdala and hypothalamus). A combination of several mechanisms including primarily alterations in the nose, neural sensitisation, and psychological mechanisms must be contemplated as a mechanism of impact.

Various discoveries in persons with odour hypersensitivity could imply that a **subgroup** of people among us are born with or have acquired an ability to be sensitised by environmental factors. Bell (1995) is of the opinion that low concentrations of a chemical create physical and psychological symptoms in especially sensitive persons, who may be genetically predisposed for affective illnesses. This hypothesis has not been corroborated, but many research results support the theory indirectly.

If it is correct, one can expect that among a randomly chosen group of people exposed to the same chemical(s), some, belonging to this subgroup, will react more strongly than others. They will prove to be more susceptible to chemical impacts and thus candidates for developing MCS.

Olin (1999) is of the opinion that our modern age makes increasing numbers of people more susceptible to environmental impacts. The most important single factor of this change is that people are increasingly being bombarded with sense impulses and impressions, which are added to the impacts from chemical, technical, and psychogenic environmental factors already received.

Many cannot adapt to the new impacts and develop the well-known unspecific health complaints associated with MCS. Olin considers the causes of these complaints to be biological rather than psychological.

6.8 Conclusion

Definite knowledge of and scientific documentation for causes and mechanisms of illness in connection with MCS still do not exist. None of the mechanisms described have been excluded beforehand.

At present, most researchers agree on the following:

1. The mechanism is based on an interaction between one or more physiological and psychological factors and
2. MCS is primarily seen in persons, who react more readily to external environmental impacts than others.

The following hypothesis can be put forward: The illness mechanism behind MCS involves both physiological and psychological impacts on certain brain centres in particularly predisposed persons.

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[3] ***Individual determined response (IDR)***: Somatic manifestation of an emotional response to an external or internal stimulus.

7 Methods of examination and diagnosis

7.1 Methods of examination

The following is a short resumé of the methods used the most for diagnosing MCS in the US today. They have to do with finding and using biomarkers for exposure, effects and incidence. Biomarkers are among the most important tools for investigating the impacts of environmental factors on health. They can indicate changes in biological systems and/or environmental illnesses such as MCS.

Biomarkers for exposure indicate that a certain exposure has taken place. The chemicals, which the body has absorbed, or derivatives thereof in blood serum, urine or tissue samples, are measured. ***E.g.,*** analytical methods have been devised to detect biomarkers in connection with exposure to heavy metals and a large number of organic chemicals such as formaldehyde, aromatic hydrocarbons, pesticides, dioxins, and PCBs and for complex exposures to, ***e.g.***, tobacco smoke.

Biomarkers for effect indicate quantitative and qualitative changes in the functioning of organs or the health of exposed persons, ***e.g.***, changes in lung function, genotoxic effects on extracted tissue samples, propagation or extrusion of inflammatory cells, or signal substances in tissue samples or urine and/or blood samples.

Provocation tests in special provocation chambers, so-called climate chambers, are MCS-specific. The climate chamber was developed by environmental and other physicians to investigate and treat MCS patients and for indoor climate research. The high technical and scientific standards[4], which are set for the construction, maintenance and running of climate chambers, make climate chambers very expensive (Selner, 1996). In the US, three well-known research centres use climate chambers for MCS and GWS research.

In Denmark climate chambers are found at the Danish Technical University, at the National Institute of Occupational Health, and at the Institute of Occupational and Environmental Medicine at the University of Aarhus.

These climate chambers are only used for indoor climate research and not for examining or treating MCS patients.

At the Department of Oto-rhino-laryngology at the Copenhagen University Hospital (Risgshospitalet) the physicians have performed "open" provocation experiments with xylene. The reaction in the vestibular organ (Vestibular autorotation test, VAT) and other physiological parameters (blood pressure and pulse) are measured before, during, and after provocation. The test was developed as a tool for screening for MCS. Normal values are based on values from a reference group. Provisional results show agreement between positive VAT and MCS in 80% of the cases. The method has not been fully standardised and should be developed further. Provisional results have been presented at a conference (Holmelund, 1993).

7.2 Diagnosing MCS

As long as MCS has not been recognised as a disease using scientific medical criteria, the condition cannot be registered in the International Classification of Diseases version 10 (ICD-10) of the WHO. It is, therefore, not included in the Danish medical statistics.

In the US an initiative group consisting of 34 physicians and researches from several fields, who have dealt with MCS problems for many years, have put forward a proposal for how to get out of the logjam concerning MCS diagnostics in the US (Consensus, 1999).

The proposal includes a

- standardised clinical definition, and a
- clinical protocol for examinations.

The clinical definition includes six items of which five have been approved by 89 clinicians and researchers (36 allergologists, 23 occupational physicians, 20 clinical ecologists, 10 specialists in internal medicine and oto-rhino-laryngology respectively (Nethercott, 1993). The initiative group proposed the sixth item.

Table 7.1 Six criteria for a clinical definition of MCS

1.The symptoms can be reproduced by repeated chemical exposure. 2.The condition is chronic. 3.Low concentrations (lower than previously tolerated by the patient) produce health complaints. 4.The health complaints improve or disappear when the source of exposure is removed. 5.Various non-related chemicals produce health complaints. 6.Symptoms of illness pertain to several organs (added in 1999).

The group proposed that the MCS diagnosis is certain when all six criteria are met, even when other illnesses (such as asthma, migraine, chronic fatigue syndrome, ***etc***.) are present.

The group also puts forward concrete proposals for a ***clinical protocol*** and for a ***research protocol***. The proposal contains a possibility for combining research into several illnesses.

Table 7.2 Proposal for a clinical protocol

1.Approved screening questionnaire 2.List of alternative illnesses for differential diagnosis 3.List of clinical signs and abnormal values from clinical-chemical parameters (published in ***peer reviewed*** literature) even though they are not commonly accepted as biomarkers for MCS 4.Following up of all MCS cases using qualitative and quantitative methods

Table 7.3 Proposal for a research protocol

1.MCS criteria for choosing the patient group (inclusion – exclusion criteria shown) 2.Full description of the examined patient groups (those ill and controls) 3.Registration and reporting of overlaps with other environmental illnesses

Ashford and Miller (2002) published a standard form with ten questions on health complaints, chemical intolerance, changed living conditions due to symptoms, ***etc***. to register environmental load and chemical sensitivity.

Kutsogiannis and Davidoff (2000) developed a simple biometric questionnaire to register MCS-related issues within six areas, such as symptoms, type and duration, exposure, sensitivity to odours and to other factors, ***etc***., easily. This method could be suited for registering Danish conditions. By relatively simple means, it would be possible to confirm or refute, whether among those previously exposed to solvents some persons with typical MCS symptoms can be found.

7.3 Comments and conclusion

Several methods to confirm or refute the MCS diagnosis have been proposed (***e.g.,*** bioimmunoassays, electronic registration of brain functions, questionnaire survey), but none have as yet proven satisfactory.

The Danish health-care system includes no guidelines neither for examination nor for diagnosis of MCS. This chapter contains some proposals as inspiration for future investigations in Denmark.

It is important that Denmark acquires better knowledge of MCS and is able to keep up to date concerning developments in environmental illnesses and MCS.

Firstly, Danish criteria defining the illness, and possibly ways in which to register the illness, should be worked out.

[4] A climate chamber must be constructed of non-synthetic materials in order to eliminate degassing. A climate chamber must have over pressure and fresh-air ventilation with filters. The furniture is made of natural, not synthetic materials. The personnel must use non-dry-cleaned clothes and neither perfumes nor scented cosmetics.

8 How MCS is dealt with by the authorities

8.1 The US and Canada

8.1.1 Regulation and recognition

Overview of previous activities in the US

Annex E gives an overview of measures and initiatives taken by authorities and private organisations with three principle aims: research into the causes of MCS, recognition of MCS in social legislation, and efforts of prevention during the period 1979-1996.

On Annex E:

Politicians, courts and the social authorities have recognized MCS pro forma, and current legislation gives patients with MCS the right to various social benefits due to their illness. This has been effected through court rulings in several US states. The court of appeal in California has ruled that one person's illness (MCS) was caused by many years of exposure to polychlorinated biphenyls, and that he should be compensated.

In 1989, the Directorate of Social Services in the US put MCS on the list of illnesses that give the right to disability benefits. As part of a warning system

in connection with outdoor spraying with pesticides, ten states in the US have passed a bill to establish a "register of persons sensitive to pesticides" (Langley, 1995).

The physicians and scientific societies were initially against, or hesitated to take part in, research connected with MCS. In California, the local medical association counteracted a bill on MCS research passed by parliament, so the governor ultimately annulled it. The Board for Environmental Science and Toxicology under the National Academy of Sciences has not followed the recommendation from the academy to implement research into MCS. From 1990 the physicians group were more willing to participate in government activities, most of which were mediated via the ATSDR (see chapter 3).

In 1994 the government in the state of Washington established several medical centres for diagnosing and treating chemical illnesses (Langley, 1995). This initiative was followed by a scientific foundation of 1.4 million US$ for research, ***e.g.***, in MCS.

The last important government action concerning MCS was to establish the intersectorial working group with the task of writing a report on current knowledge of MCS (Interagency rapport, 1998).

Present practice

The ***US Environmental Protection Agency (EPA)***, which is responsible for the external environment, seldom receives enquiries concerning MCS.

The US EPA has been deeply involved in MCS research projects for many years, especially in connection with indoor air pollution. The administrative focus is mainly on dissemination of information rather than regulation, follow-up and other control activities.

The US EPA has cooperated closely with the health authorities and with the ATSDR for many years in their support of MCS research, but at present there are no new plans concerning chemicals and MCS.

National Institute for Occupational Safety and Health (NIOSH)

Every year, the NIOSH, which is responsible for the working environment, receives several hundred enquiries concerning MCS via a free information service. The NIOSH issues information material on MCS and makes workplace assessments on demand if requested by employees, management or authorities. There are no new activities concerning MCS.

Canada, previous activities

On two occasions, the health authorities in the province of Ontario and the Dominion Government initiated MCS research and at the same time supported MCS patients in 1985 and 1990 (see Annex E).

The first Division of Environmental Medicine in Canada was established in the province of ***Nova Scotia***, in the beginning of the 1990s. During a two-year period, more than 500 employees from the local hospital were examined due to indoor climate problems. In the course of seven months many had developed chemical hypersensitivity, including MCS. Because a majority was of the opinion that odours were among the most common triggering factors, the health authorities, in collaboration with the hospital management and the labour union, issued a ban on perfume and scent-containing products in the hospital. The ban was implemented and followed up in a "soft" manner with good results (Fox, 1999).

Later, several schools and the public transport services took similar initiatives. The Union of Perfume Producers and Dealers opposed a ban on perfumes in schools, on the grounds that the cause of MCS had not been proven. The initiative group pointed to the fact that odours contribute to a deterioration of indoor air quality and can cause asthma in children, which is common in Nova Scotia. The ban was not effectuated. Many schools have, themselves, initiated an odour-free environment and have had good experience with the effort.

This is an example from Canada of a decentralized, interdisciplinary and intersectorial effort to prevent MCS, with the participation of labour unions and the people. The background material available shows that the Canadian authorities concentrate on prevention by focusing on scents.

Health Canada (HC), present practice

The health authorities have been willing to recognise three environmental illnesses (MCS, chronic fatigue syndrome, and fibromyalgia), even though their existence has not been proven objectively. As a part of the process of recognition, the patient associations were to meet at a conference with, ***e.g.***, the cosmetics industry and medical specialists. Since the patient association, however, would not meet with the industry, HC gave up its plans.

A committee in the Canadian Parliament is still exerting pressure to get MCS recognised as an illness, in order to find solutions to the social problems experienced by many people with MCS.

The Town Council of Ottawa supported a local initiative to limit the private use of pesticides in order to prevent MCS.

The industry and dealers of perfumes and cosmetics set up a cooperative body together with their partners in the US to establish an information campaign warning against closing the cosmetics industry on the basis of undocumented, doubtful proof of connections between MCS and odours.

8.1.2 Conclusion

In the US and Canada ways were found at state and province levels to deal with MCS patients with compensatory and social problems, and examination and treatment facilities were established.

The central authorities in the US took part in and supported the medical research having to do with MCS and they actively disseminated information on MCS. But the background material shows that interest in MCS is dwindling. The authorities are now focusing more on the Gulf War Syndrome.

In Canada the health authorities seem more disposed towards a "normalisation" of the recognition of environmental illnesses, than in the US. No new initiatives have been taken regarding MCS research. ***Health Canada*** is preparing a proposal, tightening regulations on perfumes and chemical products. And, together with the environmental authorities, the Canadian health authorities have taken part in decentralized initiatives for prevention.

Most of the MCS patients in the US and Canada are, of course, examined and treated at the so-called clinical-ecological centres dispersed in both countries. Although precise information is lacking, it seems that many clinical-ecological centres in Canada are cooperating more closely with the established health service than is the case in the US.

Patient organisations in Canada have had some success taking action for odour-free environments.

8.2 Europe

8.2.1 Regulation and recognition

In connection with the preparation of this report, several European countries (Norway, Sweden, Finland, Germany, The Netherlands, England, Ireland, France, Austria, Belgium) as well as the environmental agencies or administrations concerning the control of chemicals in Canada and the US were asked for information on the present policies regarding the MCS problem, possible strategies, and ideas and plans for new initiatives.

All except Austria and Belgium responded. MCS is known in all of the countries, but it is not recognised in any of them as a disease in its own right.

The ***Environmental Chemicals Unit*** under the British Ministry of Health (now Department of Health), which is a special committee composed of selected experts, has gone through all available literature on MCS. It did not find sufficient evidence to express an opinion on possible disease mechanisms or

to recommend further research on the subject. The committee recommended future developments on MCS to be followed closely.

MCS was not recognised as a disease in any of the countries contacted, and no preventive activities were going on. The environmental authorities in several countries referred to the country's expertise/authority in environmental medicine (Sweden, Germany, The Netherlands), while Ireland, England, and France referred to their occupational health authority or institute. The inquiries were perhaps sent on because they had not been sent to the proper authorities, or because in some countries it was unclear who is the proper authority to deal with this relatively new and controversial matter.

The Swedish authority in environmental medicine has performed a nation wide investigation of the incidence of MCS (results not received). The authorities in Germany have divided responsibilities between the Ministry of Health, which is responsible for the clinical definition of MCS, and the Federal Environment Ministry, which is responsible for the effects of chemicals on health in connection with MCS[5]. Both ministries get technical support from the Robert Koch Institute (National Institute of Health) and ***Umweltbundesamt*** (the environmental protection agency) respectively.

Annex H has a list of investigations of MCS, which were terminated or were still in progress in 2002. These investigations were to map the causes and the course of MCS, and act as quality control for and evaluate the methods used for investigation, diagnosis and treatment.

The German Ministry of Health is strengthening the examination and treatment capacity for environmental illnesses, including MCS.

The French Institute for Working environment ***(Institut National de Recherche et de Sécurité,*** INRS) knows MCS by the name of ***Syndrome d'intolérance aux odeurs chimiques (SIOC),*** and examination, diagnosis and treatment is done at occupational medicine hospital wards (see also section 4.1).

8.2.2 Other activities

Sweden and Germany are exceptional in having clinical-ecological centres for environmental illnesses.

Several "Ambulanz" centres for the examination and treatment of patients with environmental illnesses have been established in Germany. At least once a month MCS problems are discussed in the media on the basis of opinions expressed by the patients and the Ambulanz physicians. Information from the media has made many people call on their own physicians for examination, because they fear that they might suffer from an environmental illness.

A Centre for Environmental and Occupational Stress (CEOS) in Uppsala, Sweden treats people with MCS, electricity allergy, and stress related illnesses.

8.2.3 Conclusion

Environmental authorities in other European countries know of MCS but have not done anything in particular in this respect. In Sweden and Germany the sections for environmental medicine of the health services are conducting public surveys on MCS. Both countries have clinical-ecological centres for the treatment of environmental illnesses and there is an awareness of environmental illnesses among people in general.

8.3 Conditions in Denmark

MCS does not have an official name in Denmark. Occupational physicians call it odour hypersensitivity or solvent intolerance. The condition is not officially recognised as a disease.

8.3.1 Authorities

Current rules and practices having to do with chemicals and the environment are not specifically aimed at the hypersensitivity of MCS patients towards chemicals. The current practice of the Danish Environmental Protection Agency (EPA) concerning regulation of chemicals focuses primarily on finding problematic chemicals having particularly serious health effects, such as cancer, allergy, reproductive disorders, ***etc***., with the aim of regulating these substances in order to prevent people from becoming exposed to them.

The environmental regulations, which, ***i.e.***., ensure the protection of the people against harmful chemicals in air, earth, and drinking water, also protect MCS patients to some degree, since pollution of these media must not result in smell and taste.

Several MCS patients have approached the Danish EPA, ***i.e.***, in connection with complaints concerning Rentolin, a chemical product used on wood surfaces.

Consequently, the Danish Minister for the Environment has banned its use indoors. It must be labelled for outdoor use only.

Then, on 1 February 2000 the Danish EPA issued a statutory order limiting or banning private use indoors of surface treatment agents for walls, ceilings, and floors with high concentrations of volatile organic solvents. Products with a high concentration of volatile organic solvents must be labelled: “Must not be used indoors on ceilings, walls, and floors”.

In 1999 the Danish EPA, together with the National Consumer Agency of Denmark and the Danish Government Home Economics Council produced an information leaflet on wood maintenance and the environment, which contains good advice on choice of paints, also with regard to indoor climate. In 2001 the Danish EPA, together with The Asthma and Allergy Association

issued a leaflet on choosing wood for indoor use: “Wood breathes – and so do you” (only available in Danish). The leaflet offers advice on choice of wood, which emits least chemicals to the indoor climate.

An information leaflet on chemicals in clothes, urging people to wash new clothes before use, was issued in 1999.

An information campaign called ”Do it yourself safely” was run in 2001, aimed at raising awareness of the new rules and of the importance of airing thoroughly after having painted.

The program “systematic mapping of chemicals in consumer products” includes projects for gaining more knowledge on the subject, ***i.e.***, mapping of scents in cleaning materials and other consumer products.

In 2001 the Danish EPA started a debate on the unnecessary use of chemicals such as scents in textiles and dyes in cleaning materials. The aim is to start a public debate on the extensive use of chemicals in modern society – where some chemicals are used, even though they provide no technical benefits to the products.

The Danish EPA is striving to strengthen its efforts in areas having to do with protection against effects harmful to health. This report is a first step towards gaining more knowledge concerning the hypersensitivity of certain groups of people, and towards focusing on areas where people are exposed to unnecessary chemical effects.

The Danish Working Environment Authority knows of MCS or odour hypersensitivity, but it has not dealt with the syndrome. Inquiries have been directed to the National Institute of Occupational Health (AMI), which has much experience in the health effects of indoor air pollution.

During the last 20 years, several Danish institutions have been at the forefront of indoor climate research. One of the most effective results of this research is the implementation of labelling building materials with associated rules and guidelines, which was achieved as a cooperation project between several ministries. As a first step, efforts have been focused on reducing indoor chemical and biological air pollution (especially in high concentrations).

The National Agency for Enterprise and Housing has the statutory responsibility for construction materials in buildings, and thus also for air quality indoors. The Danish Building Research Institute cooperates with the institutions mentioned above (EPA and AMI) regarding indoor climate.

The health authorities (The National Board of Health and the regional public health officers have not yet dealt with issues regarding MCS.

In its proposal for a research strategy, the Danish Medical Research Council has prioritised an area in which the needs of MCS can possibly be met: research into the importance of indoor climate for diseases of the airways and lungs, the skin, and the digestive system.

The National Board of Health has also set up an interdisciplinary working group on research into alternative treatments having to do with prophylaxis, diagnosis, and treatment which lie outside the present limits of the Public Health Service. This working group might be able to support research into the incidence of MCS in Denmark.

8.3.2 Examination of persons with odour hypersensitivity

In the 1980s many patients with special intolerance towards organic solvents were examined at the Clinic of Occupational and Environmental Medicine and the Department of Oto-rhino-laryngology at the Copenhagen University Hospital (Risgshospitalet).

An open provocation test (described in chapter 7) gave both the patient and physicians concrete results, to which they could relate: positive results showed that the patient reacted to certain odours with physiological changes. This documentation has made it easier to get social authorities to accept, ***e.g.***, rehabilitation measures. At the time, many patients were in danger of being given long-term sick leave or being fired.

Other MCS patients were examined at a county Clinic of Occupational Medicine. The examination usually revealed no certain signs of disease, and the diagnosis was odour hypersensitivity. Lung and allergy specialists know of MCS but have not been interested in examining patients with MCS.

Most medical practitioners have limited knowledge of MCS/odour hypersensitivity and are, therefore, poorly prepared to help MCS patients.

Many patients continue to feel ill and at the same time “rejected” by the Danish Health Service. They seek alternative physicians and practitioners and have founded a patient society called The Danish MCS Organisation.

8.3.3 The Danish MCS Organisation

The organisation has 225 members, all of whom suffer from MCS.

The organisation is presented in Annex F, which describes the five main aims of the organisation. Annex G describes some patients’ experiences in the Danish health care system. It is not clear, whether the members have been exposed to chemicals in their homes or at work. Plans to examine the members at the clinics of occupational medicine at Bispebjerg and in Slagelse could not be executed. The members wished to be examined in their homes, which the physicians could not do.

8.3.4 Conclusion and recommendations

MCS patients have a problem, which the authorities and the medical care system cannot tackle at present, due to lack of knowledge and because some questions relating to definition/recognition of the illness are still unanswered. MCS patients say that they lack support from the established health care service and that they cannot get support from the social services department, because the condition is not recognised as a medical disease. Many have problems being out-of-doors or in public buildings, due to exposure to odours in these places which make them ill.

Most of the known cases of MCS in Denmark have been described by occupational physicians and a few oto-rhino-laryngologists and are caused by exposure at work. Although the risk of exposure to chemicals at work is less today than previously, the risk of being exposed to high concentrations of chemicals is still there (***e.g.***, in the case of accidents or unforeseen leakages). And impacts from poor indoor climate at work still present a problem.

The labelling of building materials for a number of years has, presumably, had positive effects on the indoor climate, and thereby also on the number of MCS cases. The extent of the problems with exposure to chemicals in private homes and during off-hours is unknown.

Many Danes, in addition to those with odour hypersensitivity, are bothered byscents, which have been added to consumer products (unnecessary chemistry). In addition to the fact that the contents of chemicals in these products is unknown, the consumers also risk becoming exposed to chemicals, where they would not expect to, ***e.g.***, from dry-cleaned clothes.

The Danish EPA, the National Board of Health, The Danish Working Environment Authority, and the National Institute of Occupational Health have not dealt with MCS - except in connection with specific cases - because of difficulties in defining MCS and the many different perceptions regarding the existence of the phenomenon.

It is important that the basis for future efforts against MCS be defined. Should it be on the basis of purely medical considerations (objective medical proof of MCS) or has MCS become a public concern, even though the illness has not been recognised as such? The problem can, to some degree, be illustrated by the different attitudes towards MCS by the authorities in the US and Canada.

From a hygienic and health viewpoint, there seem to be good arguments for prophylactic measures by the authorities. The task is surely best solved through a coordinated effort from all parties.

The most essential and natural areas to focus on in order to reduce the development of MCS symptoms are:

1. To reduce the risk of exposure to chemicals in comparatively high concentrations, and then

2. to limit chemical odours in low concentrations.

Such efforts will create a cleaner and healthier indoor climate in public buildings and private homes. It is quite possible that increased efforts within existing areas of focus can reduce the chemical pressures, which will limit the development of MCS and benefit persons with MCS.

Particular attention should be paid to the special circumstances having to do with the MCS trigger phase, since reductions of already low concentrations of chemicals are expected to benefit MCS patients by reducing their complaints.

Seen in this context, the environmental authorities must use new prophylactic strategies. A general reduction of exposure to chemicals must be added to the current assessment of the hazardous effects of chemicals (at present not including MCS effects).

In connection with the prevention of MCS it is important that people in general take part in raising the awareness and decision-making concerning the use of chemicals, especially scents, in their homes and for personal use. Only through individual participation by citizens will it be possible to reduce unnecessary odour pollution in public surroundings.

This puts special demands on dissemination of information and debate-creating activities aimed at making the citizens do their part. It must be made clear to some citizens that others cannot cope with perfumes, before they realize that they must choose to show consideration. Joint initiatives among environmental authorities and citizens in Canada are described in sub-section 8.1.1.

Similar demands for new thinking about prophylactic initiatives apply to scents added to consumer goods. See the recommendations in section 9.3.

Similar considerations concerning prophylactic efforts also apply to the health and working environment fields. Several fields of action would benefit mutually from a coordination of planning and implementation, perhaps also involving other sectors.

[5] This activity is part of both ministries' common action program for environment and health within the framework of WHO's ***National Environmental Health Action Programme*** (NEHAP).

9 Summary, conclusions and recommendations

9.1 Summary

9.1.1 Aim

During the last two decades physicians all over the World, but especially in North America, have described a new illness called ***Multiple Chemical Sensitivity*** (***MCS***). Persons with this illness experience various symptoms when exposed to odours/scents in very low concentrations**,** which do not bother most people. People with MCS demonstrate no objective physical bodily changes.

The knowledge of MCS is limited in Denmark, and just how many suffer from MCS is uncertain. In connection with the planning of a focused effort against chemicals in the environment it is important to get a clearer picture of the possible causal relationships and of the incidence of MCS in Denmark.

This report gives an overview of the knowledge of and the experience with MCS by systematically going through the available literature, expert opinions, and experience in other countries and from other authorities.

The report attempts to answer the following questions:

1. Does objective documentation for MCS being caused by low concentrations of chemicals exist?
2. Are the mechanisms behind MCS documented?
3. Which chemicals and circumstances of exposure are particularly relevant for Denmark in relation to MCS?
4. What are the possibilities for prevention?

9.1.2 Description and definition of MCS

MCS has many names, it is not a well-defined illness, and other conditions present symptoms quite similar to those of MCS. These can be indoor climate symptoms, the Gulf War Syndrome, chronic fatigue syndrome, fibromyalgia, ***etc***. All these conditions are collectively called environmental illnesses. The characteristics described below, consistent with the definitions of several scientific associations and researchers, are used to separate MCS from other environmental illnesses.

MCS is usually provoked by an initial exposure to a chemical, usually in a high concentration. Then symptoms arise from several organs, in connection with exposure to chemicals in low concentration. The symptoms are often connected to an odour. Odours from several non-related chemicals can give symptoms, which disappear when exposure ceases. The symptoms can be provoked by re-exposure. If the illness is to be diagnosed as MCS, the patients must not suffer from another disease, which might be the cause of the symptoms.

Traumatic incidents (physical and psychogenic traumas or serious infections) have also been reported to elicit MCS.

During initial exposure, phase 1, exposure to a chemical changes the pattern of reaction towards chemicals. Phase 2, the “trigger” phase starts a few months later, when odours in low concentrations provoke an “attack”. In time, the number of odours provoking attacks are gradually increased to include usual ”every-day odours” such as perfumes, car exhaust, ***etc***. With time, the symptoms also increase in number. The course of events is usually chronic (a spontaneous recovery is, however, possible).

Some patients experience health complaints a few times a week and can continue working. Others experience them daily, and are forced to stop working or to cut down on their daily activities.

9.1.3 International activities and research

With support from institutions and experts in medical research, the American authorities arranged numerous expert meetings dealing with all aspects of MCS during the period 1990-1998. Several hundred scientific papers and reports from meetings on illness mechanisms and research strategies have

been published. All of the medical science organisations have put forward their official opinions in the discussion on MCS.

9.1.4 Examples of MCS

In North America most of the MCS cases are referred to exposure to pesticides and other chemicals in the home. Based on the patterns of use of chemicals in the US compared to Europe/Denmark, it can be assumed that exposure of people in general to chemicals and degassing from building materials and home furnishings is greater in the US than in Europe and especially in Scandinavia. In Europe and Scandinavia, most MCS cases are caused by exposure at work, typically where different types of organic solvents, pesticides or other chemicals are used.

Few investigations from Denmark, Sweden, and France describe MCS in persons who have been exposed to solvents. Cases of MCS due to indoor use of wood preservatives are reported from several European countries, including Denmark (Rentolin). A number of persons who complain about the indoor climate may have MCS. These are primarily persons who are bothered by odours almost everywhere, and not only in certain buildings.

Triggering factors:

Phase 1: Chemicals (primarily in high concentrations) such as organic solvents and other volatile substances (VOC substances), pesticides, hair-care products, chlorine fumes, ***etc***.

Phase 2: All types of chemicals in low concentrations (the ones mentioned under phase 1, typically gasoline, exhaust gasses, cleaning materials, perfumes, detergents, personal care product, tobacco smoke, asphalt fumes, and fumes from household articles).

9.1.5 Prevalence

The frequency of MCS among the general public in the US is 0.2-6%, according to figures based on medical diagnoses. The frequency of self-reported (subjective) symptoms due to a selection of odours is considerably higher.

The frequency of MCS among the general public in Europe has not been investigated. It is expected to be lower (at about 1%) than in the US due to less indoor use of chemicals.

Among people in the US and Europe, who have previously been exposed to solvents, a larger percentage has been diagnosed to have MCS than in the public in general. It is presumably between 1% and 12% according to figures from the US.

The prevalence in Denmark is not known, but it is assumed to be about 0.1-1%, presumably due to a pattern of use involving less exposure than in the US.

9.1.6 Possible mechanisms

Many suggestions for causal mechanisms of MCS have been put forward. Research has not yet established certain knowledge of and documentation for the causes and mechanisms of the illness. So, none of the proposed mechanisms can be excluded in advance.

The most cited mechanism of illness is the ***immunological*** one. During the first years, when MCS was described as a hypersensitivity illness, many sought an MCS-specific biomarker. There is, however, still no proof of the existence of an immunological mechanism.

Mechanisms in the mucous membrane of the nose are considered by many to be the final explanation of MCS. The terminal fibres of the olfactory nerve (nervus olfactorius) in the mucous membrane of the nose sense chemical stimulations such as smells, while chemicals act as irritants to the terminal fibres of another nerve (nervus trigeminus).

Both brain nerves transport the impulses received to brain centres along different routes, where they create different responses. It is still unclear whether both nerves are involved in the illness mechanism.

Nerve fibres from the olfactory nerve go directly to nerve centres in the brainstem. Chemical odours can create a so-called ***neural sensitisation*** of one of these nerve centres, which are directly connected to the other centres, and which influence behaviour and organs via the autonomous nervous system as well as the overriding regulation of the hormonal balance of the body.

Experiments have shown that external physical and chemical stimuli can cause sensitisation by way of a so-called "kindling"[*] manoeuvre. Certain cognitive and behavioural changes, which can fit the mechanism mentioned above, have been observed in patients with MCS. But it has not been proven directly that this mechanism causes MCS.

Another hypothesis points at ***psychological mechanisms*** as the cause of MCS. People with MCS are no doubt under psychological pressure, but whether this pressure causes or is caused by MCS is unclear. Many are of the opinion that a conditioned reflex mechanism founded on a previous trauma can explain MCS. Others point at stress and inability to "cope" as causal factors. It seems that people who are generally more sensitive to external environmental stress are at greater risk than others of developing MCS in

[*] Kindling is expressed through an experimental method for determining a change in the reaction of the nervous system to external stimuli. By repeating chemical or electrical stimulation with so low concentrations/doses that they do not provoke any response, a lowering of the dose, which triggers cramps, can be obtained.

connection with a given chemical impact. MCS is described as a process of somatization in connection under psychosocial and environmental stress.

A more recent hypothesis speaks of an initial toxic impact reducing the tolerance of organs (***toxic-induced loss of tolerance***), after which chemical odours can create abnormal responses from several organs. This hypothesis corresponds well to the actual course of events in MCS. But it has not yet been demonstrated how tolerance is lost nor how this creates MCS symptoms.

Finally, experts in ***holistic, ecological medicine*** are of the opinion that MCS is caused by a weakening of or a defect in the defence and detoxification capacity of the body towards external chemicals, which creates imbalances in the internal functions of the body. The evidence for this hypothesis, presented by the clinical ecologists, cannot be approved according to the requirements for objectivity, standardisation and quality control established by the medical sciences.

9.1.7 Methods of examination and diagnosis

Just as there is no certain diagnosis for MCS, there is no certain test to confirm or disconfirm the diagnosis. Medical experts from the US have set up scientific guidelines aimed at attaining a diagnosis of the illness and at following up on MCS patients.

9.1.8 The handling of MCS by the authorities in the US and Europe

After a decade with much research and many meetings in the US, the authorities' activities concerning MCS have slowed during recent years. The EPA and NIOSH are currently not taking any prophylactic action concerning MCS.

The health authorities in Canada were prepared to recognize MCS in spite of the lack of diagnostic certainty. But they had to give up the plan because of lack of support. The interest in MCS has also been dwindling in Canada. But decentralized activities are going on between local environmental and health authorities and the public involving voluntary reductions in the use of personal scents and scent-containing products in public places (schools, hospitals, town halls, public transport, some workplaces).

In most European countries, MCS is not so well known, and certainly not recognized as an disease. None of the environmental authorities approached were in the process of completing prophylactic activities concerning MCS. Sweden and Germany, where clinical-ecological centres for diagnosing and treating environmental illnesses are found and where the media regularly deal with these illnesses, are conducting research activities connected with MCS (frequency, illness mechanisms, and criteria for diagnosis). At present, Germany has the most active research and development program concerning environmental illnesses in general and MCS in particular.

9.1.9 Conditions in Denmark

In Denmark the expressions odour hypersensitivity and solvent intolerance are commonly used instead of MCS. The condition is not recognised as a disease in itself and is not registered. Except for occupational and environmental physicians, specialists in psychosomatic (functional) illnesses, and a few oto-rhino-laryngologists, only a few Danish physicians know anything about MCS. Mostly occupational and environmental physicians have examined patients with MCS-like symptoms. Some patients in Copenhagen, including some who have previously been exposed to solvents, have been examined at the Department of Oto-rhino-laryngology of the Copenhagen University Hospital (Risgshospitalet), using a special open provocation test. This test confirms physiological reactions to odours in MCS patients.

The Danish MCS Organisation has approached the Danish EPA concerning the reduction of scents in the environment.

The Danish authorities have not dealt comprehensively with MCS, except when approached directly.

It seems possible to direct a possible prophylactic effort from the authorities towards reducing the risk of chemical exposure (relevant for the initial phase and the trigger phase) and – as far as possible – reducing the incidence of chemical odours in low concentrations (relevant for the trigger phase). This could include regulation in certain areas, and increased dissemination of information aimed at eliminating situations, where the use of chemical products and materials leads to high exposure. It could also include more initiatives directed towards reducing the use of "unnecessary chemicals", especially pheromones.

The health authorities need to improve examination, diagnosis, treatment, guidance, and follow-up of MCS patients.

A preventive effort is also needed in the working environment. Based on the relatively few data on MCS cases in Denmark, it can be assumed that exposure at work is of special significance for the development of MCS.

Before a preventive effort is planned, a detailed mapping of several aspects concerning the use of and exposure to chemicals, their effects on health, and the extent of the MCS problem should be carried out.

9.2 Conclusions

Multiple Chemical Sensitivity (MCS), which is called odour hypersensitivity in Denmark, is a condition with many health complaints from different organs, which occurs in certain people, when they are exposed to low concentrations of chemicals. Most international experts within the field agree, on the basis of epidemiological data, that MCS is a reality.

MCS or odour hypersensitivity is not a recognized disease and is, therefore, not listed in the WHO's International Classification of Diseases, version 10 (ICD-10).

Relatively few people get MCS, which is assumed to have two phases. The first phase usually involves exposure to a chemical, most often in high concentrations. During the second phase, exposure to chemicals in low concentrations creates symptoms. These occur in various organs (the central nervous system, parts of the airways and lungs, skin, digestive system, joints, muscles, ***etc***.).

In Denmark, some of the patients at the clinics of occupational medicine fit the MCS criteria mentioned in this report. Most of these patients have probably been exposed to solvents. People, who have been exposed to considerable concentrations of other toxic chemicals at work or in their homes (pesticides, hair-care products, wood preservatives, chlorine fumes), can develop MCS. It is uncertain whether this is due to solvents in many of these products.

Many illness mechanisms, both physical and psychogenic, have been proposed. But a direct causal relationship between exposure to chemicals in low concentrations and the symptoms/effects mentioned has yet to be proven scientifically.

Much seems to indicate that MCS is usually found in persons, who are generally sensitive to external environmental stress.

MCS occurs in 0.2-6% of the population in the US. Based on preliminary estimates and on knowledge of differences in the use of chemicals, including pesticides, between Denmark and the US, the prevalence of MCS in the population of Denmark is estimated to be about 1%. Preliminary figures from occupational medicine investigations indicate that the prevalence of MCS is 1-12% among those who have been exposed to chemicals such as organic solvents and pesticides at work.

The term multiple chemical sensitivity is inappropriate, since it puts focus on causes and mechanisms, which have not been finally clarified.

In recent years several people have preferred the name **idiopathic (unknown) environmental illness** (IEI), which is a more neutral term.

In Europe the environmental and health authorities are aware of the existence of MCS, but interest in registering cases and in research into the causes of MCS has been limited. During the last couple of years, Sweden and Germany have performed large public surveys and MCS research.

9.3 Recommendations

Although great uncertainties and a great need for more knowledge concerning MCS still exist, our present knowledge indicates that MCS is a reality and that some people are particularly sensitive to exposure to low concentrations of chemicals.

It is probably impossible to cure many of the people who already have MCS. But prophylactic measures can be taken in order to avoid that more people get MCS. And the daily lives of those, who already have MCS, can be improved.

The most important overall goal must be to limit the risk of exposure to chemicals in high as well as low concentrations.

In order to prevent MCS altogether, it is important to avoid initial exposure. In this context, special attention should be given to exposure to high concentrations of chemicals, ***e.g.***, solvents evaporating from large painted surfaces and spraying in enclosed spaces with, ***e.g.***, hairspray.

A general reduction of the chemical load would also be a step in the right direction to prevent new cases of MCS and symptoms in people, who already have MCS.

Finally, it is important that we, as consumers, know when we are being exposed to chemicals, and which chemicals they are. As consumers, we can contribute to preventing ourselves and others from getting MCS by avoiding exposure to high concentrations of volatile chemicals indoors, ***e.g.***, when painting large surfaces, and by not using strong-smelling products such as perfumes and highly scented products.

At present it is difficult to focus efforts against MCS, as long as certain knowledge concerning illness mechanisms, causality and diagnosis is lacking. An effort against MCS requires more knowledge of:

1. Incidence, causality, and effect mechanisms,
2. use of chemical products containing volatile substances,
3. exposure indoors, and
4. use of volatile substances in chemical products and goods.

Based on the present overview, and on considerations of hygiene and the general viewpoint that unnecessary exposure to chemicals and unnecessary chemicals should be avoided, it seems relevant to increase efforts within the following areas:

- General reduction in the every-day use of chemicals,
- especially reduction in the use of volatile substances (including pheromones

(perfumes)) and aerosols, and
- reduction in the use of pesticides and biocides.

It seems particularly relevant to focus on the use of additives (especially perfumes) in cosmetics, cleaning materials, and surface treatments, and to focus on indoor climate problems, including evaporation from building materials and indoor furnishings, and on environments/situations involving exposure to tobacco smoke and exhausts from traffic.

By generally focusing on reducing the every-day use of chemicals, the MCS problem can contribute to the general protection of exposed and sensitive groups of people, such as children and expectant mothers, thereby preventing some additional cases of MCS. A general recognition of MCS will, hopefully, also lead to a better understanding of the MCS patients and their problems, and hereby contribute to making their every-day life easier.

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Annex A

Overview of proposals for a definition of MCS (Interagency report, 1998)

1985	***Ad hoc Committee, Ontario Ministry of Health (1985):*** ***More than 3 months duration*** ***Multi-system disorder*** ***Intolerance to foods, chemicals, environmental agents at levels generally tolerated by majority*** ***No objective physical findings; no consistently altered laboratory test*** ***Symptoms diminish with avoidance; recur with exposure.***
1987	***Cullen (1987):*** ***Multiple chemical sensitivities is an acquired disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. No single, widely accepted test of a physiological function can be shown to correlate with symptoms.***
1991	***Ashford and Miller (2. ed. 1998):*** ***The patient with a multiple chemical sensitivity can be discovered by removal from the suspected offending agents and by re-challenge, after an appropriate interval, under strictly controlled environmental conditions. Causality is inferred by the clearing of symptoms with removal from the offending environment and recurrence of symptoms with specific challenge.***
1992	***American Academy of Environmental Medicine (1992):*** ***Ecologic illness is a chronic multi-system disorder, usually poly-symptomatic, caused by adverse reactions to environmental incitants, modified by individual susceptibility and specific adaptation. The incitants are present in air, water, food, drugs, and our habitat.***
1992	***National Research Council (NRC), Workshop on Multiple Chemical Sensitivities, Working Group on Research Protocol for Clinical Evaluation:*** ***Symptoms or signs related to chemical exposures at levels tolerated by the population at large that are distinct from such well recognized hypersensitivity phenomena as IgE-mediated immediate hypersensitivity reactions, contact dermatitis, and hypersensitivity pneumonitis.*** ***Sensitivity may be expressed as symptoms and signs in one or more organ systems*** ***Symptoms and signs wax and wane with exposures.*** ***It is not necessary to identify a chemical exposure associated with the onset of the condition.*** ***Pre-existent or concurrent conditions (e.g. asthma, arthritis, somatization disorder, or depression) should not exclude patients from consideration.***
1992	***Association of Occupational and Environmental Clinics: Workshop on Multiple Chemical Sensitivity, Working Group on "Characterizing Patients" (1992):*** ***A change in health status identified by the patient*** ***Symptoms triggered regularly by multiple stimuli*** ***Symptoms experienced for at least 6 months*** ***A defined set of symptoms reported by patients*** ***Symptoms that occur in three or more organ systems***

	Exclusion of patients with other medical conditions (psychiatric conditions are not considered exclusionary).
1993	***Nethercott (1993):*** ***The symptoms are reproducible with exposure.*** ***The condition is chronic.*** ***Low-level exposure results in manifestations of syndrome.*** ***Symptoms improve or resolve when incitants are removed.*** ***Responses occur to multiple, chemically unrelated substances.***
1995	***Kurt (1995):*** ***The symptoms are "odour-triggered" and "exposure perceived" at very low levels, but are manifest as a multitude of neurobehavioral symptoms that correspond to the accepted definitions of panic disorder.***
1996	***International Program on Chemical Safety (IPCS) (1996):*** ***An acquired disorder with multiple recurrent symptoms; associated with diverse environmental factors tolerated by the majority of people; not explained by any known medical or psychiatric disorders.***

Annex B

Recommendations from three working groups under the NRC Workshop 1991
(Interagency report, 1998)

Clinical Evaluation working group:

- Prospective longitudinal studies of exposure-based events are very important and should be performed.
- A research priority should be the study of the adaptation - de-adaptation hypothesis, and the study should be pursued using an ECU. In addition, a second approach should evaluate individuals, over time, in their usual environment.
- Selection of research subjects should be based on the specific hypothesis to be tested (***e.g.***, symptom-based, exposure-based, and population-based).
- Development of a database of chemicals, foods, drugs, and signs and symptoms reported to be associated with MCS is important.

Exposures and Mechanisms working group:

- Studies should include a comprehensive history, including exposures, physical examination, and appropriate laboratory testing. Endpoints for response should include immunological, neurological, endocrinological, psychological, social, and other markers or measures.
- Dose-response relationships should be examined.
- Animal models should be developed that mimic the human syndrome.
- Tissues obtained by biopsy and necropsy from patients, animals, and their controls should be evaluated for signs of pathologic change.

Epidemiology working group:

- The magnitude of the problem caused by MCS in the general population should be determined.
- Multi-centre, clinical case-comparison studies in occupational/environmental medicine clinics should be an early priority.
- A broad set of symptom prevalences should be utilized that will allow flexible construction of a variety of case definitions.
- Population-based methods, including construction of survey instruments, should be used to determine the basic descriptive epidemiology of certain multi-organ disorders that have been linked to MCS (***e.g.***, systemic lupus erythematosus, scleroderma, multiple sclerosis, and somatization disorder).
- Prompt studies of defined populations subjected to discrete and sudden chemical exposures should be enacted to assess the initiation and natural history of sensitivity syndromes involving environmental chemicals.
- Normal ranges for new test modalities, including the sensitivity and specificity of screening techniques and biomarkers, should be determined.

Annex C

Main proposals from the NIEHS conference on experimental research in MCS 1996 (Interagency report, 1998)

Key Recommendations:

- Studies should be initiated to test hypotheses in the domain of non-neurogenic inflammation, determining whether inflammation is present in symptomatic tissues of patients who have MCS and if it is associated with a heightened neurosensory response.
- Conduct longitudinal studies to test hypotheses:

(1)

A psychoneuroimmunological component is correlatively or causally associated with development of MCS, and

(2)

Stress is associated with MCS as a chronic disabling disease.

- Conduct double-blind placebo-controlled challenge studies performed in an environmentally controlled hospital facility coupled with rigorous documentation of both objective and subjective responses.
- Conduct interviews with MCS patients to ascertain episodes consistent with a learning interpretation of their symptoms.
- Conduct balanced placebo-controlled studies to separate the effects of chemical expectation from chemical effects in MCS.
- Evaluate the possibility of olfactory hypersensitivity in MCS patients through further research.
- Systematically evaluate the efficacy of systematic desensitisation as a treatment for MCS disorders.
- Consider single-case designs as an alternative to group comparisons, given the heterogeneity of subjects, symptoms, and chemical exposures.
- Develop a generally accepted structured interview that is based on common patterns of patient symptoms.
- One design for protocols to initiate and test for sensitisation in MCS patients could involve the same sensitisation procedures but compare outcomes under conditions of masking and unmasking.
- Test the hypothesis that MCS patients are more susceptible to initiation of context-dependent sensitisation than are control subjects.

- Longitudinal studies with repeated measures would enable evaluation of fluctuations over time.
- Conduct laboratory animal studies to assess neural time-dependent sensitisation mechanisms.

Annex D

List of recommendations for MCS research (Interagency report, 1998)

Recommendation	*NRC 1991*	*AOEC 1991*	*ATSDR [1] 1993*	*ATSDR [2] 1994*	*CDHS 1994*	*NIEHS 1995*	*EOHSI NIEHS [3] 1996*
Basic epidemiology	*X*	*X*	*X*	*X*	*X*		*X*
Case-comparison studies	*X*	*X*		*X*	*X*	*X*	*X*
Definition development	*X*	*X*	*X*	*X*	*X*	*X*	
Challenge studies	*X*	*X*	*X*			*X*	*X*
Studies of exposed pop. Incidents	*X*	*X*			*X*		*X*
Studies in ECU	*X*	*X*	*X*				*X*
Neurological research		*X*	*X*	*X*			
Olfactory research		*X*		*X*			*X*
Study of clinical ecology hypotheses	*X*	*X*					*X*
Case registries		*X*	*X*				
Determine epi. of related conditions	*X*			*X*			
Animal studies	*X*						*X*
Federal interactions			*X*				
Immune research				*X*			
Studies of therapies		*X*					
Inventory causative factors	*X*						

[1] ***Expert Panel Meeting;***

[2] ***Chemicals and Neurobiologic Sensitivity Meeting;***

[3] ***Environmental and Occupational Health Sciences Institute/National Institutes of Environmental Health Sciences Meeting.***

Annex E

Public activities in relation to MCS 1979 – 1996 (USA and Canada) (from Hileman, 1991)

***1979**: U.S. District Court for the District of Hawaii rules MCS disabling and orders the Department of Health, Education, and Welfare to provide Social Security disability benefits to an individual (Slocum vs. Califano).*

***1984**: A California bill to require research on MCS is passed by both houses of state legislature, but is opposed by California Medical Association and vetoed by Gov. Deukmajian.*

***1985**: "Report of the Ad Hoc Committee on Environmental Hypersensitivity Disorders" prepared by the Ontario Ministry of Health, Canada, calls for research on MCS and assistance for MCS patients.*

***1986**: Oregon Court of Appeals orders workers' compensation benefits for furniture store employee on basis of MCS (Robinson vs. Saif Corp.).*

***1987**: National Academy of Sciences (NAS) workshop recommends research on MCS, with assistance from the Institute of Medicine and the National Institutes of Health, to ensure that fundable proposals are developed; NAS Board on Environmental Sciences and Toxicology takes no action on recommendations.*

***1987**: California Court of Appeals awards workers' compensation benefits to employee who was found to have MCS resulting from long-term exposure to polychlorinated biphenyls (Kyles vs. Workers' Compensation Appeals Board).*

1988: State of Maryland directs funds for a chemical hypersensitivity study conducted by R. Bascom.

***1988**: Social Security Administration adds section on MCS to agency's program operations manual for disability determinations.*

***1989**: Ashford and Miller prepare a report on MCS for the New Jersey State Department of Health.*

***1989**: Indoor Air Quality Act introduced in Senate addresses MCS.*

***1989**: Ohio Court of Appeals reinstates an order of the Ohio Civil Rights Commission finding unlawful employment discrimination for dismissal of an employee with MCS (Kent State University vs. Ohio Civil Rights Commission).*

***1990**: Department of National Health and Welfare in Canada convenes a workshop on MCS to develop priorities for research into MCS and to identify the health needs of MCS patients; report is issued in January 1991.*

***1990**: Pennsylvania Human Relations Commission orders a landlord of an MCS patient to take measures to accommodate her, including reduction in the use of pesticides (Atkinson vs. Lincoln Realty).*

***1990**: Office of Technology Assessment declines to include the issue of MCS in its report on immunotoxicological research needs.*

***1991**: At request of EPA, Division of Indoor Air, NAS organizes a workshop of invited experts on MCS; research recommendations are developed.*

***1991**: The Association of Occupational and Environmental Clinics (AOEC), under the sponsorship of ATSDR, organizes a meeting to focus primarily on the clinical aspects of the condition.*

***1992**: Department of Housing and Urban Development recognizes MCS as a disability requiring reasonable accommodations under the Fair Housing Act Amendments and the Rehabilitation Act of 1973.*

***1992**: As a part of the Fiscal Year 1993 budget process, Congress mandates ATSDR to utilize $250,000 for "chemical sensitivity/low-level chemical and environmental exposure workshops."*

***1993**: ATSDR, addressing a Congressional mandate, convenes a panel of experts to offer guidance on initiatives it should undertake, given the current state of knowledge and the resources available.*

***1994**: ATSDR convenes a national meeting in Baltimore to consider the neurobiological aspects of chemical sensitivity.*

***1995**: State of Washington designates $1.5 million research fund for chemically related illness.*

***1996**: A workshop organized by the International Program on Chemical Safety meets in Berlin; majority of participants suggest "idiopathic environmental intolerances" (IEI) to replace the term MCS.*

(Interagency Report, 1998)

Annex F

May we present:

The Danish MCS Organisation

(Founded February 1994)

The main objectives of the organisation are (from the organisation regulations):

1. To disseminate information and knowledge of odour and chemical hypersensitivity,

2. to give odour and chemical hypersensitive people advice and guidance (help them to help themselves),

3. to fight for a clean environment and cleaner air,

4. to convince The National Board of Health/the legislators of the importance of odour and chemical hypersensitivity research,

5. to fight for a long-term solution to our indoor climate problems - especially odour-free waiting rooms, hospital wards, nursing homes, ***etc***. - and encourage the building of allergy-friendly homes,

6. recognition of our illness and full pensions for those not able to work, and

7. to contribute to the establishment of a diagnosis and treatment centre.

Briefly about the illness:

Multiple Chemical Sensitivity differs from allergies in that antibodies cannot be traced in the skin, in mucous membranes or in the blood. The term hypersensitivity or chemical intolerance is, therefore, more appropriate.

The condition/illness is not recognised as an illness in Denmark, which is probably due to the lack of diagnostic parameters. Awareness from the media is, therefore, very important to this patient group, in order for them to be able to put pressure on/inspire relevant health persons.

The character and extent of the illness has not been investigated in Denmark. But American physicians estimate that about 4% of the population in North America suffer from this illness. By a rough estimate, this would mean that about 200,000 persons in Denmark would to some extent have symptoms (one or more), if “appropriately” exposed.

Symptoms: fatigue, irritated mucous membranes in eyes, nose, and throat, headache, dizziness, concentration difficulties, memory and learning difficulties, breathing difficulties, palpitation, arthralgia, depression, and many more (varies from patient to patient).

Causes: chemicals that reach our mucous membranes via the air around us and create violent and aggressive reactions in the “nervous system”.

The concentrations of these substances are often far lower than those ”normal” individuals would notice.

The chemicals can be so-called natural substances or they can be synthetic.

Examples of every-day elements that can create symptoms in odour and chemical hypersensitive persons:

Tobacco smoke, frying odours, wood smoke, perfumes, deodorants, after-shave, washing powder and softener, newspapers, advertising brochures, photocopying machines, self-copying paper, disinfectants, ***etc***., ***etc***.

Consequences: Persons suffering from odour and chemical hypersensitivity experience difficult situations with odours in the busses, trains, offices, cinemas, restaurants, medical laboratories, churches, libraries, public swimming baths, ***etc***., ***etc***., ***etc***. - in other words in all of the places where people meet and exchange odours and argue about who smells the best.

For many, having the symptoms described above leads to disabling social isolation.

The Danish MCS Organization attempts, to the best of its ability, to act as spokesman for the socially isolated and encourages everyone with symptoms of this disease to join the organisation.

The more we are, the better we can work to establish a better and wider understanding of our everyday problems. At the same time we can increase our efforts regarding the health system.

We look forward to co-operating with an understanding and communicating press at all levels.

Kind regards on behalf of the organisation,

Flemming Obling

Should you wish to contact the organisation for further information, or if you wish to receive comments on events with relation to our handicap, then you are welcome to contact one of the persons below.

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Annex G

Summary of descriptions by members of The Danish MCS Organization

Most members have experienced how humiliating it is to be the object of suspicion and regarded as a psychiatric case. The organization and its members have information on MCS from international sources. But general practitioners usually do not want to read this information, in spite of the fact that they know nothing about the definition of the illness, methods of examination, and treatment. They can regard their patients as being "obsessed" by their illness.

The organization has sent some case histories supporting the course of events described above to the Danish EPA. A physician at Ambulanz in Rostock diagnosed a member as having MCS and many accompanying signs of illness that were to be investigated further and treated in Denmark. Again, the Danish specialists were not very keen on carrying out the investigations, which had been prescribed by a physician in Germany, specialized in environmental illnesses. They could see neither the need nor the use of such an investigation.

Martin Silberschmidt

15.10.2001

Annex H

Overview of the activities on MCS under the German ministries of Environment (BMU) and Health (BMG) (in German) (from: Umweltsbundesamt für Mensch und Umwelt, Dr. J. Dürkop, Berlin, 2001)

Übersicht über die im Rahmen des ***Ufoplan*** des BMU geförderten MCS-Vorhaben (Stand: 08.10.2001)

Lfd. Nr.	Förderkennzahl	Thema	Bearbeitungsstand	Laufzeit	Bemerkungen
1	298 62 274	Untersuchungen zu Ursachen des MCS-Syndroms unter besonderer Berücksichtigung des Beitrages von Umweltchemikalien	Abgeschlossen	01.02.1999 – 30.06.2001	Verbundstudie (Probandengewinnung = Erstuntersuchung) Abschlussbericht in Vorbereitung
2	201 61 218/04	Globalansatz APUG. ***Teilvorhaben:*** Studie zum Verlauf und zur Prognose des MCS-Syndroms – Erweiterung der Basisstichprobe und Nachuntersuchung (Folgevorhaben)	Läuft	01.08.2001 – 31.12.2003	Verbundstudie (Follow up = Nachuntersuchung + zusätzliche Probandengewinnung = Ersterhebung)
3	200 61 218/02	Globalansatz APUG. ***Teilvorhaben:*** Untersuchungen zur Suszeptibilität bei multipler Chemikalienüberempfindlichkeit (MCS)	Läuft	01.01.2001 – 30.04.2003	Zusatzprojekt (Enzympolymorphismen bei Probanden der Verbundstudien)

Übersicht über die durch das BMG zum Thema "Umwelterkrankungen" geförderten Vorhaben (Stand: 08.10.2001)

Lfd. Nr.	Förder-kennzahl	Thema	Bear-bei-tungs-stand	Laufzeit	Bemer-kungen
4	328-1720/48	Langzeit-verlauf und Versorgungs-regime von ambulanten und stationären Patienten der Umwelt-medizin	Läuft	20.11.2000 – 20.11.2002	
5	328-1720/49	Evaluation eines Ansatzes zur Behandlung toxisch belasteter Personen: eine kontrollierte Therapie-studie	Läuft	20.11.2000 – 30.11.2002	
6	328-1720/35	Umwelt-bezogene Erkran-kungen (Berliner Studie)	Abge-schlos-sen	01.04.1998 – 31.05.2001	Abschluss-bericht in Vorbe-reitung
7	328-1720	ZEBUM Zentrale Erfassungs- und Bewer-tungsstelle für umwelt-medizinische Methoden	Läuft	01.11.1998 – 31.12.2001	

Kommission des Robert Kock-Instituts

8	328-1720/38	RKI-Kommission „Methoden und Qualitätssicherung in der Umweltmedizin"	Läuft	Ab 01.09.1999	