Organic solvent exposure and neuropsychiatric disorders : results from an epidemiological study among Dutch painters and construction workers

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Organic solvent exposure and neuropsychiatric disorders

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Results from an epidemiological study among
Dutch painters and construction workers

Proefschrift

ter verkrijging van de graad van doctor
aan de Rijksuniversiteit Limburg te Maastricht,
op gezag van de Rector Magnificus, Prof. Dr. F.I.M. Bonke,
volgens het besluit van het College van Dekanen,
in het openbaar te verdedigen
op donderdag, 9 november 1989 om 14.00 uur

door

Cornelis van Vliet
geboren te Noordwijkerhout in 1959

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CHAPTER 1

INTRODUCTION

INTRODUCTION

The aim of the study presented in this dissertation is to elucidate the role of exposure to organic solvents with respect to the occurrence of premature disability due to neuropsychiatric disorders among Dutch painters. Painters are occupationally exposed to organic solvents as these chemicals are an essential part of most paints and lacquers. The question whether long-term exposure to organic solvents eventually results in the development of neuropsychiatric disorders originates from the Scandinavian countries. The wide spread use of organic solvents together with the alarming results from Scandinavian countries have resulted in a world-wide interest into this matter.

A brief historical review may clarify the reasons why an epidemiological study, investigating the neuropsychiatric effects of organic solvent exposure as experienced by Dutch painters, has been carried out in The Netherlands.

In 1979 the Dutch painters branche joined the Dutch Organization for the Improvement of Working Conditions in the Construction Industry (Stichting Arbouw). Apart from organising occupational health service for the construction industry, this organization stimulates scientific research concerning health problems related to working conditions. Consequently several studies were started to evaluate the health risks of the painting profession. The most remarkable finding emerged from a study into absenteeism of painters in the construction industry. Compared with other construction workers, painters had a 35% increased risk for being prematurely disabled due to neuropsychiatric disorders.

These results were rather alarming and, in view of the results from Scandinavian countries, the question was raised whether this increased occurrence of neuropsychiatric disorders among painters was caused by organic solvent exposure.

Clearly, the absenteeism study could not answer this question, because, apart from organization membership, no information was available about the organic solvent exposure of the compared groups.

Furthermore, information about other factors related to the etiology of neuropsychiatric disorders (such as alcohol consumption, headtrauma, other diseases) must be known in order to make a fair comparison between two groups with respect to the occurrence of neuropsychiatric disorders. Therefore a new study was initiated in order to evaluate the relationship between organic solvent exposure and neuropsychiatric disorders. This study started in 1985 at the Department of Occupational and Environmental Health and Toxicology of the University of Limburg in Maastricht.

Financial support was given by the Stichting Arbouw. The Dutch Painters and Construction Workers Organizations co-operated in this study by providing the possibility to approach persons receiving disability benefits due to neuropsychiatric disorders.

The results of this study were edited into articles and subsequently submitted to relevant medical journals. Therefore, 9 chapters of this dissertation are based upon articles which have been submitted to or published in medical journals. A disadvantage of this approach is that some sections of the relevant articles/chapters will inevitably show some overlap and repetitions. An advantage is that these chapters can be read separately.

The second chapter of this dissertation provides a review of the (epidemiological) literature with respect to neurotoxic effects of organic solvent exposure. The study design used in the presented epidemiological study is described and discussed in Chapter 3.

Chapter 4 shows the results of a study into medical files of persons prematurely disabled due to neuropsychiatric disorders. The next chapters reveal the results of a case-control study conducted among Dutch painters and construction workers. The overall risk for painters to be prematurely disabled due to neuropsychiatric disorders is presented in Chapter 5, while Chapter 6 deals with the analysis concerning dose-response relationships. Special attention is given to the occurrence of neurotic disorders among Dutch painters (Chapter 7). The occurrence of pre-narcotic and neurasthenic symptoms among solvent exposed workers is presented in Chapter 8. Chapter 9 reviews all epidemiological studies (including our own study results) investigating the relationship between organic solvent exposure and premature disability due to neuropsychiatric disorders. Next, a chapter called "summary and concluding remarks" reviews the results as described in the preceding chapters (Chapter 10).

A Dutch article about the results of this study, simultaneously meant as a Dutch summary, concludes this dissertation (Chapter 11).

CHAPTER 2

THE ORGANIC SOLVENT SYNDROME AMONG PAINTERS: FACT OR FICTION*

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ABSTRACT

This review article deals with the question whether long-term exposure to organic solvents may lead to irreversible damage of the central nervous system, like the "organic solvent syndrome". The exposure of painters to organic solvents and the relevant epidemiological literature are discussed. The discrepancy between the results of studies from Scandinavian countries and other countries, such as Great Britain and West-Germany, attracts attention. The obscurity of the underlying pathophysiological mechanism, the lack of uniformity in the diagnosis of the organic solvent syndrome, methodological shortcomings and the absence of a clear dose-response relationship in many studies complicate the interpretation of the epidemiological data.

Based on currently available epidemiological data the central question of this review article cannot be answered with a straightforward yes or no. This restriction applies in particular to occupational exposure to low concentrations of organic solvents (i.e. below the MAC-values).

INTRODUCTION

The Dutch painters population consists of approximately 35,000 persons¹. Painters are an important group of workers within the construction industry who, due to the nature of their work, are exposed to all sorts of potentially harmful chemicals². Organic solvents, which are an important ingredient of many paints and lacquers, belong to these potentially harmful chemicals.

For some time concern exists among occupational physicians about the long-term health effects of exposure to organic solvents. This concern includes exposure to concentrations below the Dutch MAC-value (maximum allowed concentration of gas, vapour, spray or of a chemical in the air). Particularly Scandinavian scientists suggest a relationship between long-term exposure to organic solvents and irreversible harmful effects on the central and peripheral nervous system³. In this review article first of all attention is paid to some general characteristics of organic solvents and the way in which painters are exposed to these chemicals. Next, the acute and chronic neurotoxic effects attributed to organic solvent exposure are described and the literature with respect to these effects is

reviewed. Emphasis is given to epidemiological studies of humans in which attention is focussed on neurotoxic effects of long-term occupational exposure to organic solvents.

The article concludes with a discussion of some problems with regard to human epidemiological research of chronic neurotoxic effects due to organic solvent exposure.

ORGANIC SOLVENTS

Organic solvents are defined as "at room temperature or moderately increased temperature volatile liquids in which other liquids/gasses and/or chemicals are dissolved (molecularly divided). Furthermore, during or after dissolution, no chemical reaction takes place between the solvent and the dissolved chemical"⁴.

Organic solvents are used at large scale⁵:

- To dissolve and to dilute paint, lacquer, synthetic resin, rubber, glue and printing ink;
- To degrease and to clean metal objects (e.g. as pretreatment for welding) and textile ("dry cleaning");
- to extract fats and oils from vegetable materials;
- as basic chemical or additive in chemical synthesis;
- as coolant;
- as anti-freeze;
- as pesticide;
- as narcotic;
- as fuel;
- as anti-knock;
- as basic chemical in pharmaceutical and cosmetic industry.

The use of organic solvents is not restricted to certain occupations. Furthermore, organic solvents are frequently used in hobbies and housekeeping. Organic solvents as a group consist of compounds with a great diversity of chemical structures. Table 1 gives a frequently used classification of organic solvents.

Table 1: Classification of organic solvents

-
1. Hydrocarbons (mostly technical mixtures):
 - Boiling point gasolines
 - White Spirits; mineral spirits
 - Cycloaliphatic hydrocarbons
 - Benzene, toluene, xylene
 - Aromatic solvents with higher boiling points
 - Terpenes
 2. Halogenated hydrocarbons
 3. Nitrogenous hydrocarbons
 4. Alcohols
 5. Aldehydes
 6. Ethers
 7. Esters
 8. Glycols and glycolethers
 9. Ketones
-

In connection with the volatility of organic solvents, the airways are the most important absorption route in humans. However, uptake through the skin is also possible. The rate of admission and transfer to depots (various lipoid tissues) depends on the partition coefficient between blood and air of the concerning solvent. A high partition coefficient facilitates uptake and transfer to depots. The concentration of solvents in the brain shall rapidly increase because of the high blood flow in the brain compared to subcutaneous fat. The main excretion route of solvents is through the airways. A low participation coefficient between blood and air facilitates a rapid excretion⁵. Sometimes solvents are metabolised to more water soluble products, thus facilitating excretion by the kidneys or the liver.

Painters are exposed to organic solvents, since these chemicals are an important part of many paint products. The Dutch paint industry consumed in 1979 26,300 tons terpenes, which brings these solvents on top of the list of much-used solvents. In The Netherlands hydrocarbons constitute 40% of the organic solvent use. Doorgeest et al⁴ do not expect a drastical change of this percentage within the next five to ten years. The mostly used hydrocarbons are mixtures, e.g. white

spirit consists of more than a hundred different hydrocarbon compounds. Exposure of painters to organic solvents depends on various factors, such as⁴:

- Type of paint product;
- Composition of the paint product;
- Daily applied amount of paint, lacquer etc.;
- Working conditions (e.g. ventilation);
- The use of respirators;
- Personal hygiene.

The chemical department of the Dutch National Labour Office and TNO have carried out measurements in the painting trade of organic solvent concentrations in the ambient air. Both personal air sampling and stationary measurements were used. These measurements showed that only incidentally individual measurements exceeded the MAC-value (= Dutch TLV-value). The exposure index, calculated by adding up the quotients of the detected concentrations and MAC-values of the various solvents to which one was exposed, turned out to be more often elevated (= above 1). However the health implications of an increased exposure index are still uncertain⁴. Measurements from the past are virtually not available. As apparent from the above information, determination of the nature and level of organic solvent exposure among painters is not a simple matter. Furthermore, important changes have occurred in the composition of paint products during the last decades⁴.

HEALTH EFFECTS DUE TO ORGANIC SOLVENT EXPOSURE

The health effects of exposure to organic solvents can be divided into acute and chronic effects. Effects on the central nervous system play an important role, but are certainly not the only potential health effects of organic solvent exposure.

Acute health effects of organic solvents are⁵:

- Degreasing and dehydrating effects on the skin;
- Irritating effect on the mucosa of eyes and airways;
- Acute chemical pneumonia after uptake of liquid solvents in the lungs;

Chronic health effects are:

- Peripheral neuropathy (e.g. n-hexane);

- Blood anomalies, including leukaemia (benzene);
- Effects on liver and kidney (e.g. chlorinated hydrocarbons).

The neurotoxicity of organic solvents depends on their lipid solubility by which they can pass the blood-brain barrier. Furthermore, as mentioned before, the high blood flow through the brain facilitates the development of high concentrations in the central nervous system. The first description of neurotoxic effects due to organic solvent exposure dates from 1856. In that year August Delpech described a psychotic syndrome among some workers from a rubber factory who were exposed to carbon disulfide (CS_2)⁶. Next, in the first decade of this century a neurasthenic syndrome was described among workers occupationally exposed to trichloroethylene, xylene and white spirits³.

The neurotoxic effects of organic solvent exposure can be divided into acute chronic effects. The acute neurotoxic effects are represented by the contact syndrome⁵. The severity of the symptoms is determined by the momentaneous exposure to organic solvents. The narcotic effects (diminution of the level of consciousness) dominate this syndrome. The severity of this syndrome varies from a slight diminution of the level of consciousness to death. An important characteristic of this syndrome is the rapid reversibility once exposure has ceased. In view of this effect it is not surprising that a lot of organic solvents have been used as anaesthetics⁷. The narcotic effect is preceded by prenarcotic symptoms, such as drowsiness, nausea, dizziness, headache, drunken feeling, alcohol intolerance and incoordination⁸.

The (sub)chronical neurotoxic effects of long-term exposure to organic solvents are (from times) divided in two syndromes^{5,9,10}:

a) Subchronical syndrome.

Beside prenarcotic symptoms the following complaints occur in this syndrome: fatigue, sleeplessness, nightmares, stomach and precordial pains, ear tingling and paraesthesia. The severity of this syndrome is also dependent on the exposure duration and the complaints cease after a few days or weeks.

b) Organic psychosyndrome.

The organic psychosyndrome consists of chronic disturbances in psychological functioning. The main symptoms are fatigue, slow and inaccurate perception, memory and concentration disturbances, emotional lability, depressive complaints and personality changes. This syndrome was thought to occur after long-term exposure.

Apparently forty years ago⁹ scientists were aware of the possibility of the occurrence of chronic neurotoxic effects due to organic solvent exposure. How-

ever, the assumption was made that these chronic neurotoxic effects only occurred among workers with long-term exposure to very high concentrations of strong neurotoxic solvents (e.g. CS_2). The notion that moderate or low exposure to organic solvents, such as white spirits, as experienced by painters could induce serious damage to the central nervous system originates from Sweden³. In a Swedish hospital a striking number of house painters was seen, who complained of extreme fatigue, memory disturbances, loss of appetite and precordial pains. Subsequently, several investigations were carried out among Scandinavian painters and other workers who were exposed to organic solvents. On the basis of the results of these studies (which will be discussed later) Scandinavian scientists came to the conclusion that organic solvent exposed workers, particularly painters, are at increased risk for the development of an organic psychosyndrome, also designated as organic solvent syndrome. The organic solvent syndrome manifests itself by a great number of (aspecific) complaints, such as forgetfulness, diminished ability to concentrate, diminished comprehension, emotional lability, depression, fatigue, headache, diminished coordination⁴. The organic solvent syndrome is an officially recognized occupational disease in the Scandinavian countries. Criteria have been formulated to diagnose this syndrome. In these criteria emphasis is put upon anamnesis (history of exposure to organic solvents, presence of neurasthenic complaints) and the results of neuropsychological investigations (Table 2).

Table 2: Diagnostic criteria for organic solvent intoxication¹¹.

-
1. Verified quantitative and qualitative exposure to solvent known to be neurotoxic.
 2. Clinical picture of organic damage to the central and/or peripheral nervous system:
 - "Typical" subjective symptoms;
 - Pathologic findings in some of the following:
 - * Clinical neurological status;
 - * Electroencephalography;
 - * Electroneuromyography;
 - * Psychological tests.
 3. Other organic diseases reasonably well excluded (by neuroradiological methods, special laboratory investigations or follow-up if necessary).
 4. Primary psychiatric diseases reasonably well excluded.
-

The organic solvent syndrome has been given several different names in the international literature, such as organic brain syndrome, chronic encephalopathy, pre-senile dementia, painters syndrome, neurasthenic syndrome and Scandinavian syndrome. This lack of uniformity hampers the interpretation and comparison of the investigations as well as the international collaboration in the field of chronic neurotoxic effects due to organic solvent exposure¹¹.

In order to solve these problems, the World Health Organization established a working group to study the neurotoxic effects of organic solvent exposure. The working group stated that the chronic effects could be divided into two different syndromes, an "organic affective syndrome" and a "chronic toxic encephalopathy". Characteristics of these syndromes are presented in Table 3¹¹.

Table 3: Classification schemes of chronic neurotoxic effects attributed to organic solvent exposure.

I World Health Organisation¹¹:

- An organic affective syndrome, predominated by disorders of mood.
- A chronic toxic encephalopathy that may be mild or severe. This syndrome is characterised by a change in personality, accompanied by "core symptoms" of fatiguability, bad memory, difficulties in concentration and loss of initiative.

II Working group North Carolina¹³:

- Type 1 : Non-specific symptoms such as fatiguability, bad memory, difficulties in concentration and loss of initiative.
 - Type 2A: Pronounced and sustained change in personality denoted by fatigue, emotional lability, alterations in general mood etc.
 - Type 2B: Difficulties in concentration, impairment of memory and a decrease in learning capacity. These symptoms (unlike those in 2A) may be accompanied by objective evidence of impairment. There may also be minor neurological signs.
 - Type 3 : Marked global deterioration in intellect and memory (dementia). Often accompanied by neurological signs and/or neuroradiological findings.
-

A few months later, a working group in North Carolina evaluating the same neurotoxic effects, came up with a completely different classification of the syndromes thought to be attributed to organic solvent exposure. This classification

was not primarily based on specific syndromes as shown in Table 3^{6,12,13}. The above described course of affairs illustrates that the organic solvent syndrome is still not well defined and/or internationally accepted as an existing syndrome or occupational disease.

EPIDEMIOLOGICAL INVESTIGATIONS INTO CHRONIC NEUROTOXIC EFFECTS

Most studies into chronic neurotoxic effects of long-term exposure to organic solvents have been carried out in Scandinavian countries. Painters and workers from the paint industry were shown to have more neurasthenic complaints than workers from non-exposed control populations^{8,14-16}. Furthermore, painters had a tendency to score worse on neuropsychological testbatteries than workers from non-exposed control populations^{8,15,17-19}.

Some investigators detected anomalies in electroencephalograms of exposed workers^{15,16,20}. A number of investigators found brain atrophy and/or a decrease in the bloodflow of brain tissue among patients diagnosed with an organic solvent syndrome^{15,21,22}.

It is hardly surprising that, in particular in Scandinavian countries, the question was raised whether chronic neurotoxic effects due to organic solvent exposure could lead to premature disability. This issue is addressed in three Scandinavian case-control studies and one Scandinavian cohort study²³⁻²⁶. It appeared from these studies that workers exposed to organic solvents are at increased risk for being prematurely disabled due to neuropsychiatric disorders.

Study results showing no indications for the existence of an organic solvent syndrome mainly originate from countries outside Scandinavia. Cherry and Waldron²⁷ found no indications for a relationship between neuropsychiatric disorders and organic solvent exposure in Great Britain. Furthermore Cherry et al²⁸ detected no differences between neuropsychological testscores of painters and a control group of non-exposed workers. However, the painters did report more neurasthenic complaints. Triebig et al²⁹ concluded that the organic solvent syndrome does not occur among German construction painters. Maiszlish et al³⁰ could not demonstrate neurological anomalies among a group of solvent exposed workers. The study of Orbaek et al³¹ did not indicate the existence of brain atrophy among a group patients diagnosed as having an organic solvent syndrome. Some recently published case-control studies did not reveal a relationship between organic solvent expo-

sure and the development of dementia³² or mortality due to presenile dementia³³. From a Swiss cohort study emerged no significantly increased risk for painters (compared to electricians) to become disabled due to neuropsychiatric disorders. Besides, alcoholism appeared to be an important factor in the development of neuropsychiatric disorders among painters³⁴. In The Netherlands Scheffers et al³⁵ carried out a study into absenteeism of painters in the construction industry, by order of the Dutch Organization for the Improvement of Working Conditions in the Construction Industry (Stichting Arbow). They compared the absenteeism statistics of the Dutch Painters and Construction Workers Organizations. Attention was paid to the number of cases reaching the maximum payment period of the Dutch health law (= 52 weeks) during the period 01-01-1975 to 31-12-1977. Diagnoses were coded according to a national list of disease classification based on the 9th revision of the International Classification of Disease. Neuropsychiatric disorders appeared to occur 35% more often among painters than among construction workers.

DISCUSSION AND CONCLUSIONS

This review article deals with the question whether long-term occupational exposure to organic solvents may lead to irreversible damage of the central nervous system. To answer this question attention must be paid to the quality and the validity of the conducted studies. Several authors place critical comments at all evidence put forward in favor of the organic solvent syndrome.

Grasso et al³ are particularly sceptical in their review article. They point out that many of the used neurological examinations (neuropsychological tests, EEG's etc.) are not suited to be applied in epidemiological studies. Frequently, there is uncertainty about for example the reference values, reproducibility, interpretation of the results and the influence of other factors on the test results.

In case of a causal relationship between exposure to organic solvents and chronic effects on the central nervous system, one may assume that the risk of developing these chronic neurotoxic effects increases with higher levels of organic solvent exposure. However, many studies do not reveal a positive dose-response relationship. As mentioned, measurements from the past are virtually not available and painters are generally exposed to mixtures of organic solvents. Furthermore the dose of organic solvent exposure is frequently expressed as "number of exposure years", which is of course a poor and inaccurate reflection of the exposure intensity.

Remarkably follow-up studies show little improvement or deterioration in the condition of painters diagnosed with an organic solvent syndrome as the exposure to organic solvents has ceased³⁶. According to Grasso et al³ this fact is inconsistent with the hypothesis that long-term exposure to organic solvents is responsible for the development of an organic solvent syndrome. After all, the condition of patients with an electromyographically proved neuropathy improves after disappearance of the exposure, while the condition of persons diagnosed with other neurodegenerative diseases, such as Morbus Alzheimer, deteriorates in due course of time.

Waldron⁶ pointed to other obscurities with respect to the organic solvent syndrome. An oppressive question concerns the differences between e.g. Denmark, where hundreds of painters have been diagnosed as having an organic solvent syndrome and countries outside Scandinavia in which this syndrome is hardly recognized. Recently Errebo-Knudsen and Olsen³⁷ and Gade et al³⁸ stated that many Danish painters were wrongly diagnosed as suffering from an organic solvent syndrome. When reference values were determined of the used neuropsychological test-methods in well chosen control populations, the scores of many painters appeared to be within the normal population distribution of the test scores. Ekberg et al³⁹ suggested that the neurasthenic complaints and abnormalities in neuropsychological investigations as detected among solvent exposed workers merely reflect acute neurotoxic effects. Many investigations have been carried out among exposed workers who actively participated in the labour process, thus being daily exposed to organic solvents.

The complaints reflecting chronic neurotoxic effects attributed to organic solvent exposure are rather non-specific. The same complaints may be caused by other factors and disorders, such as alcohol abuse, stress, aging, head trauma, lead intoxication etc. It is essential to take the influence of these potential confounders into account in the analysis of the data and interpretation of the study results¹³. Many studies fail to handle this issue adequately. Correction for e.g. differences in age and alcohol abuse between exposed and non-exposed groups has been carried out, but the influence of e.g. workstress as confounding factor has not yet been evaluated in this context.

However, the criticism stated above applies to both the positive and negative studies.

Diagnostic criteria, as formulated in the Scandinavian countries, show that the "organic solvent syndrome or intoxication" can only be diagnosed by exclusion⁴⁰. However, it is very difficult to exclude all other possible causes of the complaints. Therefore it is not surprising that follow-up studies show that for some

persons other causes of their complaints emerge in due course of time⁴¹. The underlying pathology of this syndrome remains unclear^{6,12}. Is there actually a loss of neurones or do other (biochemical?) changes occur in the brain tissue of patients diagnosed with an organic solvent syndrome? There is an urgent need for an animal model for further research with respect to this syndrome⁶. The choice of the control population in the Scandinavian disability pension studies can be criticised. The control population consisted of persons disabled due to non-neuropsychiatric disorders. If non-exposed workers are at increased risk for developing these disorders (e.g. more disorders of the musculoskeletal system among brick layers because of carrying heavy cement bags) compared to organic solvent exposed workers, an overrepresentation of non-exposed persons will occur among the control population. Thus, the observed risk for exposed persons to be disabled due to neuropsychiatric disorders would be wrongly increased⁴². Probably another limitation of these disability studies is the lack of reliability of diagnoses awarded by social security physicians to people receiving disability benefits⁴³. This limitation (at random misclassification) tends to mask existing relationships⁴⁴.

The investigation of Scheffers et al³⁵ of absenteeism of painters in the construction industry has some weak points. They mention in their publication a few shortcomings of their study design. The main objections are the lack of a longitudinal component and the absence of information concerning nature and duration of organic solvent exposure of the persons included in the absenteeism statistics. Furthermore the results were not adjusted for confounding factors, such as education level and alcohol consumption.

All these critical remarks, together with some negative results from studies conducted outside Scandinavia, indicate that at the moment no certainty exists with respect to the presence of a causal relationship between long-term occupational exposure to organic solvents and the development irreversible damage to the central nervous system. This lack of clarity concerns especially occupational exposure to organic solvents in concentrations below or hardly exceeding the MAC-values. The presence of a harmful effect due to long-term exposure to high concentrations of organic solvents is more plausible. Obviously individual differences may be present with respect to the susceptibility to the neurotoxic effects of organic solvent exposure. Undoubtedly a lot of research has to be done on the field of the health effects of organic solvents which were already designated by Delpech in 1856 as "a foul and pestile congregation of vapours".

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CHAPTER 3

ORGANIC SOLVENT EXPOSURE AND NEUROPSYCHIATRIC DISORDERS; DESIGN OF AN EPIDEMIOLOGICAL STUDY.*

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MOTIVATION OF THE STUDY DESIGN

The central issue of this study is whether organic solvent exposure, as experienced by Dutch painters leads to an increased risk for being prematurely disabled due to neuropsychiatric disorders. To test a hypothesis, the epidemiologist may use experimental and observational studies. In experimental studies persons must be exposed intentionally to the potential toxic agent, which from an ethical point of view yields prohibitive objections.

With regard to observational studies, a choice must be made between cross-sectional and longitudinal study designs. Considering the time factor enclosed in the central question, a cross-sectional study design is less suitable. Therefore a choice must be made from the observational study designs. Observational longitudinal epidemiological research has two approaches. The investigator may compile a group of exposed and a group of non-exposed workers. These groups then are followed for a certain period of time in order to determine the occurrence of morbidity or mortality in the relevant groups. This so-called cohort study design starts from the specific health-threatening exposure, e.g. exposure to organic solvents.

Case-control studies follow a reversed approach. The starting point of a case-control study is a group of persons with a certain disease ("cases") and a group of persons without the disease under study ("controls"). Next, the frequency of the occurrence of a (potential) causal factor among the cases is compared with the occurrence of the relevant factor among the controls¹.

Both approaches have specific advantages and disadvantages. If the epidemiologist is interested in a wide range of health effects due to one specific exposure, a cohort study is the approach to be preferred. If the objective of the study is to investigate a wide range of causes and factors that may play a role in the development of a specific disease, a case-control study is the most obvious choice. The aim of this study is to investigate the relationship between a specific disease (neuropsychiatric disorders) and a specific exposure (organic solvents). In this case the choice of study design can be based on other considerations. Oftenly efficiency considerations are of additional importance. Cohort studies are more extensive, more expensive and more labour intensive than case-control studies. In view of the above mentioned arguments we have chosen for a case-control study design².

POPULATION BASE

The first step at the start of a case-control study is to define the population base, that is the population from which cases and controls will be selected. This case-control study has been carried out among workers affiliated to the Dutch Painters Organization (SFS) and Construction Workers Organization (SFB). The SFB was founded in 1952 by employers and employees in the construction industry. In broad outlines, the assignments of the SFB can be divided in three parts:

- Collection of contributions and insurance money;
- Management of funds;
- Granting of payments and benefits.

Dredging companies and painters companies are (just like construction workers) affiliated to the industrial insurance board of the construction industry. However, these companies have not delegated the above mentioned assignments to the SFB. Instead, both dredging companies and painters companies have a separate organization that manages these tasks. Thus, the painters organization (SFS) carries out the Dutch health law and disability law for painters, while these laws are carried out by the SFB for other construction workers. However, for applications of unemployment benefits all workers (including workers of painters and dredging companies) ought to turn to the SFB.

Two kinds of considerations play an important part at the definition of the population base:

- 1) Efficiency (power) considerations;
- 2) Availability of the data.

Ad 1. Efficiency (power) considerations

It is of importance that within the population base some variability exists with respect to the exposure to the potential etiological factor (i.e. organic solvent exposure). The power, that is the statistical chance to detect an in reality existing association in a case-control study, depends on the number of cases and controls included in the study, the percentage of controls exposed (at present or previously) to the potential etiological factor and the α -level used for statistical tests. A satisfactory efficiency of a case-control study may be defined as a situation in which as few cases and controls as possible are needed to detect a certain association with a high power. The efficiency of a case-control study is optimal if about half of the controls have been exposed to the possible etiological

factor³. If the study was restricted to the SFS-population, the greater part of the population would have been exposed to organic solvents. The population base was compiled in such a way that about 50% originated from the SFS (exposed) and about 50% originated from the SFB (non-exposed). As for education and jobs a strong relationship exist with respect to certain occupations within SFS and SFB. Bricklayers, plasterers and carpenters are just like painters involved in maintenance and newbuilding activities. Moreover, painters and construction workers are frequently present at the same workstation⁴. Given the fact that the SFB is approximately seven times greater than the SFS, only one seventh of the SFB-population needed to be included in the study. This situation was approximated by including in the study workers affiliated to the SFB whose sixth digit of the registration number is a six or seven (born on day 06, 07, 16, 17, 26, 27 of any month). In this way only one fifth of the SFB-population was included in the population base. In the above considerations SFB was considered as non-exposed and SFS was considered as exposed to organic solvents. However, this is a simplification of reality since higher trained and administrative personal affiliated to the SFS may not have been exposed to organic solvents. On the other hand the SFB-file contains painters and other construction workers, e.g. road markers, who are also exposed to organic solvents. Thus, the construction workers and painter organizations are impure with respect to the exposure to organic solvents. During the case-control study information of the exposure to organic solvents of all participants will be collected by questionnaires.

Ad 2. Availability of the data

The preparation of the case-control study was complicated by the fact that SFS and SFB have separate and different registration systems. Data of both registration systems ought to be combined in order to compile one file of workers (painters and construction workers) from which cases and controls could be collected. With reference to the sampling of the control population it was desirable to have computer prints of all registration numbers of the included population base. After intensive consultation with SFS and SFB on this matter, it was decided to use the following files:

SFS: The population base from which cases and controls were selected consisted of male workers affiliated to the SFS who built up rights (holiday allowance and/or pension claims) between 25 April 1984 and 25 April 1985.

Since April 1983 a so-called "painters coupon" is used by the SFS. This coupon includes a vacation bonus, a risk fund bonus and a pension bonus. Most workers of the painting trade receive with their payments a painters coupon in accordance to regulations from the collective labour agreement of the painting trade. The worker can cash the vacation bonus of these coupons by submitting the coupons, together with a payment request to the local representative of the SFS. Painters submitting a payment request are centrally registered at the SFS. The collective labour agreement does not apply to a small group of workers (mainly administrative) within the painters trade. The persons involved receive no painters coupons, but do pay pension contributions. These pension contributions are also centrally registered. The population base was compiled by combining the "payment request file" and the "pension claim file". These files are drawn up at the end of each coupon year (from April to April) and include data from the entire preceding year.

This population includes:

- Persons who have left the painting trade by the end of the coupon year, but who worked in the painting trade for some period during the preceding coupon year;
- Persons receiving benefits according to the Dutch health law;
- Persons receiving partial benefits from the Dutch disability law.

A computer print of this population base was supplied by the SFS at 24 October 1984. This print consisted of 35,811 registration numbers.

SFB: The population base from which cases and controls were selected, consisted of male workers included in the so-called RBS-system (Rechten Beheer Systeem) of the SFB between April 1984 and April 1985, whose sixth digit of the registration number is a 6 or 7.

The RBS-system of the SFB started in 1983 and replaced the coupon system. In this system the employer transfers the rights of his workers (such as holiday bonus, pension and risk fund contributions) every four weeks to the SFB. These rights are entered on the account of the workers. Once a month the workers receive a survey, indicating their balance. The data included in the RBS-system are related to the preceding year.

This population includes:

- Persons who have left the construction trade by the end of the RBS-year, but who worked in the painting trade for some period during the preceding RBS-year;

- Persons receiving benefits due to the Dutch health or unemployment law (including painters!);
 - Persons receiving partial benefits from the Dutch disability law.
- The SFB supplied a computer print of the RBS-population base on 28 August 1985. This print consisted of 38,079 registration numbers.

POWER CALCULATION

Originally it was intended to include as many controls as cases in the study. Based on the assumption that 400 cases would participate in the study, 400 controls ought to be selected. Based on these numbers (400 cases and 400 controls) the power of this study to detect a relative risk of 1.4 for exposed workers compared with non-exposed workers to develop neuropsychiatric disorders was calculated to be 80%.

During the conduct of the study, it became clear that the number of cases participating in the study remained significantly below the expected number of 400 cases. Therefore it was decided to increase the number of controls included in the study to prevent a decrease of the study power. The size of the control population was increased to 1,000 persons to preserve a power of 80% based on the participation of 250 cases.

DEFINITION OF CASES AND CONTROLS

Cases

Cases were defined as male persons from the population base receiving disability benefits due to neuropsychiatric disorders as from a date between 01-07-1984 and 01-07-1986 (incident cases).

Illness of a worker is reported by the employer to the Organization (SFS or SFB) to which he is affiliated. In case of recovery within 2 to 4 weeks the insured patient is generally visited once or more by a rapporteur (= employee of the SFS or SFB, who is not a physician). If no recovery occurs within this period the

patient must contact a social security physician (= medical adviser of SFS/SFB) or visit him during office hours. Social security physicians organised in regional medical departments are engaged in patient counseling of both painters and construction workers. The maximal duration of benefits under the Dutch health law is 52 weeks. After this period patients may be eligible for disability benefits. In The Netherlands the disability pension system has its legal basis in a specific disability act. Patients who are eligible for a disability pension (i.e. who will probably exceed the period of 52 weeks) are examined by medical advisers of the GMD (= Gemeenschappelijke Medische Dienst). They determine the degree of disability which is important for the magnitude of the disability benefits granted after 52 weeks of illness. Granting of disability benefits is not related to the question whether working conditions have lead or contributed to the development of the disease. Social security physicians of the GMD will make a diagnosis for all examined patients. Diagnoses are converted to diagnostic codes by specially trained nosologists. Diagnoses are coded according to a list based on the International Classification of Diseases, 9th revision (Appendix 1). Neuropsychiatric disorders are classified under group V. Since the end of the seventies the Federation of Dutch Industrial Insurance Boards use also a list of diagnostic codes based on the ICD-9.

Patients suffering from an organic solvent syndrome will, based on the nature of their complaints (see Chapter 2), probably be diagnosed under:

- ICD 300: neurotic disorders;
- ICD 309: adjustment reactions;
- ICD 311: depression, not elsewhere classified.

Since it is assumed that this syndrome reflects the presence of organic brain damage, the correct ICD-code for these patients would probably be ICD-310 (specific non-psychotic mental disorders following organic brain damage). However, the organic solvent syndrome among painters is no officially recognized syndrome or occupational disease among Dutch physicians.

Preceding the case-control study, a cross-sectional study of medical files was carried out to get a clear insight in the neuropsychiatric disorders occurring among painters. Medical files, kept by social security physicians, of painters and construction workers receiving disability benefits due to neuropsychiatric disorders were compared with respect to the occurrence of diagnoses and neuropsychiatric complaints. Possibly the results of this file study would permit to restrict the case-control study to specific ICD-codes within the group of neuropsychiatric disorders.

The results of this file study, as reported in Chapter 4, together with the above described considerations lead to the decision to include initially all neuropsychiatric ICD-codes (group V) in the study. Next, during the analysis of the data a distinction could be made between ICD-codes in all probability more (300, 309, 311) or less frequently awarded to persons suffering from the organic solvent syndrome.

Cases originated from the population base of SFS and SFB workers, as described earlier. Consistent with this description SFB-cases must fulfill an additional criterion, i.e. the sixth digit of their registration number must be a six or seven.

Controls

The control population consisted of a representative sample from the population base, taking into account differences in size and age distribution between SFS and SFB.

Table 1: Age distribution of the population base and of the randomly selected stratified control sample of 1,000 persons.

Year of birth	SFS			SFB			Total		
	n	(%)	Number of controls	n	(%)	Number of controls	n	(%)	Number of controls
1915-1919	0	(0.0)	0	4	(0.0)	0	4	(0.0)	0
1920-1924	217	(0.6)	3	334	(0.9)	5	551	(0.7)	8
1925-1929	693	(1.9)	9	1,344	(3.5)	18	2,037	(2.6)	27
1930-1934	1,734	(4.8)	23	2,470	(6.5)	33	4,204	(5.7)	56
1935-1939	2,345	(6.5)	32	3,467	(9.1)	47	5,812	(7.9)	79
1940-1944	3,340	(9.3)	45	4,475	(11.8)	61	7,815	(10.6)	106
1945-1949	5,521	(15.4)	75	6,180	(16.2)	83	11,701	(15.8)	158
1950-1954	6,073	(17.0)	82	5,939	(15.6)	80	12,012	(16.3)	162
1955-1959	6,115	(17.1)	83	5,791	(15.2)	78	11,906	(16.1)	161
1960-1964	6,828	(19.1)	93	5,511	(14.5)	75	12,339	(16.7)	168
1965-1969	2,945	(8.2)	40	2,564	(6.7)	35	5,509	(7.5)	75
Total	35,811	(100.0)	485	38,079	(100.0)	515	73,890	(100.0)	1,000

The computer prints with registration numbers as delivered by the SFS and SFB served as the starting point for the selection of controls. In total these prints contained 73,890 registration numbers. The first six digits of the registration number constitute of the date of birth (year/month/day). Thus the age distribution of the SFS and SFB-population could be calculated from these prints. Sampling was performed with lists of aselect numbers⁵. Table 1 shows the age distribution, converted into "years of birth"-categories of the population base and of the stratified sample of 1,000 persons. For all control persons it was checked at the SFS and SFB whether they belonged to the group of persons included in the population base receiving partial disability benefits. None of the controls was found to receive these benefits, so the control population was build up exclusively of people receiving no disability benefits, thus being not long-term disabled.

Cases and controls were not matched with respect tot the occurrence of potential confounding factors such as age. This decision was taken in order to be able to investigate the effects of these variables on the development of neuropsychiatric disorders. Matching would eliminate the effects of the relevant variables.

Figure 1 depicts the case-control study design used in our study.

THE QUESTIONNAIRE

A questionnaire was used to collect information from the participating cases and controls. The questionnaire consisted of 44 questions (Appendix 4). The following topics were addressed in the questionnaire:

- Personal identification (1 and 2);
- Disability (3 to 6);
- Education (7 to 9);
- Occupations (10 and 11);
- Working conditions and exposure to organic solvents among painters (12 to 24);
- Exposure to organic solvents in other occupations (25 and 26);
- Work-related complaints (prenarcotic symptoms) (27 and 28);
- State of health (29 to 33);
- Symptoms fitting the 'organic solvent syndrome' (neurasthenic symptoms) (34);

Figure 1: Schematical presentation of de case-control study design.

- Potential confounding variables: - Quetelet-index (35);
- Alcohol consumption (36);
- Smoking (37)
- Workstress and private stress (38 to 43).

A pilot study with this questionnaire was carried out among 36 painters and construction workers in July 1985. This pilot study showed that the questionnaire was easily completed by the participants and that the questions were clear and understandable.

Construction workers completed the questionnaire in an average of 15 minutes. Painters needed on the average 30 minutes to complete the questionnaire. This difference between painters and construction workers is explicable, since a number of questions are only intended for painters.

APPROACH OF CASES AND CONTROLS

Cases and controls were approached both by letter and telephone to ask them to participate in this study. The choice for a combined approach (by letter and by telephone) was made to achieve a high response (i.e. percentage of the approached persons participating in the study).

The response of an exclusively written approach was expected to be around 40%, based on experiences in previous studies. A response rate of 60% was expected by adding a telephone call to the approach policy.

The approach of cases and controls took place according to the following plan:

- 1) Forwarding of a letter of introduction (Appendix 2). The object and nature of the investigation are elucidated in this letter. The study is introduced under the title: "Health and working conditions among construction workers and painters". This general title was chosen in order to reduce information bias. The letter announced a telephone call of the investigator to the (potential) participant to request co-operation in the study.
- 2) Minimally four days after mailing the letter of introduction, the investigators tried to telephone the approached cases and controls.
The following rules were kept while phoning:

- Questions about the investigation were answered as clear as possible without mentioning the relationship between organic solvent exposure and neuropsychiatric disorders;
 - In the absence of the participant, the investigator consulted, if possible, his partner or wife about participation in the study of the approached persons;
 - In case of a refusal to participate, the investigators asked for the reason.
- 3) Persons willingly to participate in this study, as agreed by telephone, were sent a questionnaire. The questionnaire was accompanied by a letter supplying some additional information about the completion of the questionnaire (Appendix 3).
- 4) If the questionnaire was not returned within four weeks the investigators made a reminder by telephone. This reminder was, if necessary, repeated after another 4 weeks.
- 5) Respondents who did not return the questionnaire after two reminders were considered as non-respondents.

RESPONSE

During the period from 01-07-1984 to 01-07-1986, 505 male persons of the study population were granted disability benefits due to neuropsychiatric disorders. Consequently 505 cases and 1,000 controls were eligible to participate in this study. The approach of potential respondents was restricted to persons who had a telephone. This decision was made after it became clear that the response rate in the group without telephone would be very low (about 20%). Since of all cases and controls information was available about their affiliation (to SFS or SFB), a comparison could be made regarding accessibility by telephone of different subgroups (Table 2).

Part of the approached persons with a telephone refused to participate in the study. This is the total number of refusers. Refusing to participate was sometimes indicated in the first telephone call (refusers I). In other cases the refusal was expressed at the telephonic reminder, or the questionnaire was not

returned in spite of telephonic promises (refusers II).

Table 3 shows the distribution of non-respondents (refusers) among the different subgroups.

Table 2: Accesibility by telephone of cases and controls.

	SFB controls	SFB cases	SFS controls	SFS cases	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
Approachable by telephone	437 (84.9)	222 (85.4)	385 (79.4)	187 (76.3)	1,231 (81.8)
Not appoa- chable by telephone	78 (15.1)	38 (14.6)	100 (20.6)	58 (23.7)	274 (18.2)
Total	515 (100.0)	260 (100.0)	485 (100.0)	245 (100.0)	1,505 (100.0)

Table 3: Co-operation of the approached persons.

	SFB controls	SFB cases	SFS controls	SFS cases	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
Co-operated in the study	311 (71.2)	134 (60.4)	262 (68.1)	118 (63.1)	825 (67.0)
Refusers I	98 (22.4)	70 (31.5)	82 (21.3)	47 (25.1)	297 (24.1)
Refusers II	28 (6.4)	18 (8.1)	41 (10.6)	22 (11.8)	109 (8.9)
Refusers (total)	126 (28.8)	88 (39.6)	123 (31.9)	69 (36.9)	406 (33.0)
Total	437 (100.0)	222 (100.0)	385 (100.0)	187 (100.0)	1,231 (100.0)

Controls not willingly to participate in this study were replaced by new controls, selected from the same organization (SFS or SFB) and birth-cohort. There-

fore the control population included in the study consisted of 822 persons. Since the total number of cases occurring during the study period was limited to 505, the same procedure could not be applied to the cases. Thus, the number of cases included in the study was restricted to 252.

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CHAPTER 4

THE ORGANIC SOLVENT SYNDROME. A COMPARISON OF CASES WITH NEUROPSYCHIATRIC DISORDERS AMONG PAINTERS AND CONSTRUCTION WORKERS.*

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ABSTRACT

A study was conducted to investigate the existence of a "specific" neurotoxic effect due to long-term exposure to organic solvents. A comparison was made regarding diagnoses, symptoms and other relevant medical data between persons receiving a disability pension on the basis of a neuropsychiatric disorder selected from an exposed (painters) and non-exposed (construction workers) trade organization. Information was collected from their medical files at the medical department. Concerning diagnoses and symptoms, no significant differences were found between exposed and non-exposed patients. No indications were found for the existence of a "typical" complex of symptoms associated with exposure to organic solvents among painters in The Netherlands. The number of reported symptoms was not related to the duration of exposure, thus lending no support for a dose-effect relationship. If a neurotoxic effect does exist among Dutch painters, it is of a non-specific type and not clearly distinguishable from other mental disorders.

INTRODUCTION

Recently substantial attention has been given to the potential neurotoxic effects of prolonged exposure to organic solvents¹. Publications, particularly from Scandinavian countries, have reported adverse neurological, neurophysiological and psychological disorders in solvent exposed workers².

Neurasthenic symptoms have been reported to be more frequent in exposed workers than in non-exposed controls³⁻⁷. The relative risk of disability pension due to presenile dementia appeared to be higher among solvent exposed workers in several epidemiological studies⁸⁻¹⁰. Some studies conducted outside Scandinavia did not support these findings. Cherry et al¹¹ found no evidence of an association between psychiatric morbidity and solvent-exposure in British workers. Triebig et al¹² conducted a retrospective casuistic study among patients examined in their clinic, who were suspected of suffering from an occupational disease. During the period 1963 to 1984 they had not seen a painter with disorders of the peripheral and/or central nervous system as an occupational disease.

This study was not designed to detect a possible increased risk of solvent expo-

sed workers for developing neuropsychiatric disorders. Instead, it focusses on the nature of the organic solvent syndrome. The syndrome thought to be caused by organic solvent exposure has been given a number of different names, such as psycho-organic syndrome, chronic encephalopathy, presenile dementia, painters syndrome, neurasthenic syndrome. Recently two attempts have been made to describe the disorders of the central nervous system that may be caused by long-term exposure to organic solvents. A WHO working group¹³ distinguished between an organic affective syndrome and a chronic toxic encephalopathy that may be mild or severe. However, four months later at a meeting held in North Carolina, another classification was suggested, implying that the condition is still not as well defined or understood as one would like^{1,13,14}.

Orbaek et al⁷ carried out a cross-sectional epidemiological study among workers in the paint industry. They stated that a clinically important neurasthenic syndrome in a patient who was exposed to solvents for at least one decade should be recognized as work-related when other important diseases have been excluded reasonably well. Juntunen^{15,16} formulated diagnostic criteria for the diagnosis of organic solvent intoxication, one of these being the existence of typical subjective symptoms. The most common symptoms observed among patients with organic solvent intoxication are: headache, memory disturbances, tiredness, dizziness, nervousness, paresthesia and concentration difficulties^{3-5,15}.

Painters are exposed to the vapours of various solvents. Riala et al¹⁷ determined the exposure to organic solvents among Finnish maintenance painters. The mean 8-h concentration of White Spirit (= a mixture of organic solvents) in the breathing zone averaged 40 ppm over the painters' total worklife. A study concerning the exposure of Dutch maintenance painters to organic solvents¹⁸ revealed exposure to C8 - C11 alkenes and C7 - C10 aromates among all painters, while incidentally alcohols, ketones, esters and chlorated hydrocarbons were detected in the breathing zone.

Although some construction workers are occasionally exposed to organic solvents we assume this exposure to be of little significance compared with painters.

The study population of the present study consists of patients diagnosed with neuropsychiatric disorders. They (all) receive a disability pension from the Dutch Painters Organization (SFS) or Construction Workers Organization (SFB). In this study a comparison has been made regarding diagnoses, symptoms and some other relevant medical data of patients from the Painters and Construction Workers Organization. The aim of this comparison was to investigate the existence of specific symptoms or syndromes among neuropsychiatric patients previously exposed to organic solvents. This study precedes the performance of a case-con-

trol study among painters and construction workers which will be carried out in order to determine whether exposure to organic solvents is associated with the risk for receiving disability benefits due to neuropsychiatric disorders.

MATERIAL AND METHODS

Dutch painters and construction workers are organised in a similar way for the execution of social laws, such as health, unemployment and disability insurances. In The Netherlands the disability pension system has its legal basis in a specific disability law. According to this law payment of disability benefits is considered after 52 weeks of illness. The disability pension is not related to whether or not the disease/injury was a result of working conditions. Local departments of social security physicians engaged in granting of disability benefits cover the members of both organizations. Diagnoses of persons receiving disability benefits for neuropsychiatric disorders were awarded by these social security physicians. These diagnoses were coded by expert nosologists according to a list based on the International Classification of Diseases - 9th revision (ICD-9). These codes (see Table 2) were used to select male persons receiving a disability pension due to neuropsychiatric disorders. Participation in the study implied agreement to exploration of their medical files. In this case the medical file refers to the information collected by the physicians of the above mentioned medical department. From the files of the participating workers information was collected concerning age, diagnosis, occupational history, symptoms, medication and further medical history.

Informed consent was given by 239 patients receiving a disability pension due to a neuropsychiatric disorder. The number of refusals was equally divided among the painters and the construction workers organizations.

In the statistical analysis of the collected data we calculated means, standard deviations and Odds Ratio's. The Odds Ratio (OR) approximates the relative risk in case few diagnoses/symptoms appear in both the exposed and non-exposed group. Besides, the Odds Ratio as such is a commonly used measurement of association between exposure and illness (< 1 = a negative relation; 1 = no relation; > 1 = a positive relation)¹⁹. The confidence limits ($\alpha = 0.05$) of the Odds Ratio's were calculated according to Schlesselman²⁰. Student's t-test was used to define the significance of the difference between two means (Table 4).

RESULTS

A division was made between exposed and non-exposed patients, based on the occupational history of all 239 persons. Subjects, previously working as painters were classified as being exposed to organic solvents, while those who had worked as construction workers were classified as non-exposed, if it was not stated that they had been involved in painting work. The number of years worked as a painter was also known in this study. A subdivision of painters (e.g. construction painters, maintenance painters) could not be made, since this classification was missing in most files.

Table 1: Age distribution and magnitude of exposed and non-exposed persons.

Age (years)	Exposed		Non-exposed	
	n	%	n	%
19 - 29	9	9.2	9	6.4
30 - 39	24	24.5	33	23.4
40 - 49	31	31.6	41	29.1
50 - 59	22	22.4	45	31.9
> 60	12	12.2	13	9.2
Total	98	100.0	141	100.0

Table 1 shows the age distribution and number of exposed/non-exposed subjects. Mean age at first disability payment data of the exposed workers was 44.5 (SD 10.8) years compared to 45.8 years (SD 10.3) for the non-exposed workers. The mean exposure time of the painters was 24 years (SD 10.7). The mean working time of the non-exposed construction workers was 25.3 years (SD 10.2).

Physicians of the medical department of the painters and construction workers organizations coded their diagnosis according to a list based on the ICD-9 classification. Diagnoses (and codes!) can change during an illness. Therefore we agreed upon using the diagnosis/code stated in the medical file at the time of application for a disability pension.

Table 2 shows a review of the diagnoses as coded by the physicians mentioned above.

Table 2: Occurrence of diagnostic codes among the exposed and non-exposed group-
as coded by the social security physicians.

ICD- code	Description	Exposed		Non-exposed		Odds Ratio (OR)	Confidence limits of OR ($\alpha = 0.05$)
		n	%	n	%		
290	Dementia	-	-	1	0.7	-	-
295	Schizophrenic psychosis	1	1.0	1	0.7	1.44	0.09 - 23.30
296	Affective psychosis	4	4.1	5	3.5	1.16	0.30 - 4.43
298	Other non-organic psy- chosis	2	2.0	2	1.4	1.45	0.20 - 10.47
300	Neurotic disorders	29	29.6	33	23.4	1.38	0.77 - 2.47
301	Personality disorders	2	2.0	4	2.8	0.71	0.13 - 3.95
303	Alcohol dependence syndrome	1	1.0	4	2.8	0.35	0.03 - 3.81
304	Drug dependence	-	-	2	1.4	-	-
306	Physiological malfunction arising from mental fac- tors	3	3.1	13	9.2	0.31	0.09 - 1.12
307	Special symptoms or syn- dromes not elsewhere classified	1	1.0	-	-	-	-
309	Adjustment reaction	50	51.0	73	51.8	0.97	0.58 - 1.62
310	Specific non-psychotic mental disorders follo- wing organic brain damage	-	-	2	1.4	-	-
311	Depressive disorder, not elsewhere classified	3	3.1	1	0.7	5.47	0.56 - 53.38
317	Mild mental retardation	2	2.0	-	-	-	-

Schizophrenic psychosis (295), affective psychosis (296), other non-organic psychosis (298), neurotic disorders (300) and depressive disorders not elsewhere classified (311) occurred more often among the exposed group (Odds Ratio > 1). However, the differences between the exposed and the non-exposed group are relatively small and of no statistical significance.

Table 3: Frequency distribution of symptoms among exposed and non-exposed subjects.

Description	Exposed		Non-exposed		Odds Ratio (OR)	Confidence limits of OR ($\alpha = 0.05$)
	n	%	n	%		
Nervousness	74	75.5	95	67.4	1.49	0.83 - 2.67
Depressive feeling	61	62.2	80	56.6	1.26	0.75 - 2.13
Somatic symptoms	34	34.7	70	49.6	0.54	0.32 - 0.92
Vegetative disorders	33	33.7	44	31.2	1.12	0.64 - 1.97
Anxiety	31	31.6	44	31.2	1.02	0.63 - 1.66
Sleeping disturbances	29	29.6	35	24.8	1.27	0.71 - 2.26
Dizziness	22	22.5	20	14.2	1.75	0.90 - 3.42
Psychosomatic symptoms	22	22.5	38	27	0.78	0.43 - 1.43
Headache	21	21.5	30	21.3	1.01	0.54 - 1.89
Fatigue	20	20.4	26	18.4	1.13	0.59 - 2.16
Agressive behaviour	19	19.4	30	21.3	0.89	0.47 - 1.69
Concentration disturbances	16	16.3	20	14.2	1.18	0.58 - 2.41
Hyperventilation	15	15.3	14	10	1.64	0.75 - 3.57
Major psychic symptoms	14	14.3	19	13.5	1.07	0.51 - 2.25
Suicidal thoughts/behaviour	12	12.2	19	13.5	0.90	0.42 - 1.95
Numbness or parasthesia of extremities (neuropathy)	6	6.1	3	2.1	3.00	0.73 - 12.30
Memory disturbances	5	5.1	14	9.9	0.49	0.07 - 1.87

There is no evidence in the literature that the organic solvent syndrome includes disorders like psychosis, alcoholism, anorexia nervosa etc. It is mostly characterized as a neurasthenic syndrome and hence probably coded as 300 (neurotic disorders), 309 (adjustment reaction), or 311 (depressive disorders not elsewhere classified). Taking these three codes together the Odds Ratio is 1.62 (0.84 - 3.16). We could not demonstrate a dose-effect relationship in terms of an increased frequency of ICD codes fitting the organic solvent syndrome among the group

with longest (> 20 years) exposure to organic solvents.

In order to rule out coding errors by the social security physicians, the 239 cases were coded according to the ICD classification, independent of the ICD-codes given by the social security physicians. This also revealed only minor differences between the exposed and the non-exposed group.

A list was compiled of the symptoms noted in the medical files. All symptoms were grouped in 17 categories. Table 3 gives a review of the results.

Nearly all these symptoms occurred more often among the exposed patients, but here again the differences are of no statistical significance. The mean number of symptoms occurring among the exposed group was 7.0 compared to 6.3 for the non-exposed group.

In search of a possible dose-effect relationship in terms of the number of reported symptoms and duration of exposure, the two groups were divided in subgroups according to their number of working years. For each group the mean number of symptoms was calculated. As shown in Table 4 the highest prevalence occurred among the youngest painter group.

Table 4: Mean number of reported symptoms among exposed and non-exposed persons related to their number of working years.

Number of working years	Mean number of reported symptoms	
	Exposed	Non-exposed
1 - 10	8.2	5.2*
11 - 20	6.6	7.1
21 - 30	7.5	6.8
> 30	6.3	5.6

* $p < 0.05$ (Student's t-test)

Three items collected from the medical files were regarded to be indicative for the severity of the mental disorder:

- medication (use of psychopharmaca).
- admission to a psychiatric ward/hospital during the examined 52-week period prior to disability pension.
- psychiatric history (previously treated for a mental disorder).

All three items were observed more often among the exposed patients, but here again the differences between the two groups are not statistically significant (see Table 5).

Table 5: Severity indicators among exposed and non-exposed persons.

	Exposed		Non-exposed		Odds Ratio (OR)	Confidence limits of OR ($\alpha = 0.05$)
	n	%	n	%		
Psychopharmaca	56	57.2	72	51.1	1.28	0.76 - 2.14
Hospital admission	16	16.3	14	9.9	1.77	0.82 - 3.82
Psychiatric history	39	39.8	43	30.5	1.51	0.88 - 2.60

DISCUSSION

Occupational exposure to organic solvent is encountered in a range of occupations, but certainly among painters, since organic solvents are an essential part of most paints. In the present study we investigated the existence of specific neurotoxic effects of the occupational exposure to organic solvents. The medical files of patients with neuropsychiatric disorders who had previously worked as painters and construction workers were compared.

A problem in this study is the quality of the basic material. There was a potential lack of uniformity in the recording of data in the medical files. Recording of data sometimes was obviously incomplete. Furthermore random misclassification can not be excluded. However, these potential sources of bias should have affected both the exposed cases and the non-exposed cases similarly, because at the time that most cases were diagnosed no particular interest had yet been given to the organic solvent syndrome in The Netherlands. Thus, it is unlikely that report bias, over-reporting of symptoms among exposed cases or under-reporting of symptoms among non-exposed cases has affected the results of this study. Subsequently it is clear that both exposed and non-exposed cases were medically examined by the same physicians. Besides the above mentioned problems, the small number of patients and the resulting small statistical power should be remembered while interpreting the results.

In this study no significant differences were found in diagnoses (diagnostic codes) between the exposed and non-exposed patients. Mikkelsen⁹ suggested that painters are more likely to develop presenile dementia. In our study only one (non-exposed!) person received a disability pension due to dementia (ICD-code: 290). However the use of the diagnostic term "presenile dementia" differs in Denmark and The Netherlands.

Furthermore, as stated in the introduction the neuropsychiatric disorders of the central nervous system caused by long-term exposure to organic solvents are still not well defined. Possibly these two factors are responsible for the lack of differences in diagnoses between the two groups.

One of the criteria formulated by Juntunen et al¹⁵ for diagnosing organic solvent intoxication is the existence of typical subjective symptoms. The symptoms appear gradually and persist for some time following cessation of the exposure^{21,22}. A number of these symptoms (e.g. nervousness, dizziness and paresthesia) did occur more often among the exposed group. However, the differences were of no statistical significance and, surprisingly, another important symptom, memory disturbances, was more common among construction workers (the non-exposed group). Besides, one must realise that the "typical subjective symptoms" associated with the organic solvent syndrome are of a non-specific nature, and are more or less present in a number of neuropsychiatric disorders.

In case of the existence of a dose (i.e. the number of years worked as a painter) - effect relationship we would expect to find the highest prevalence of neuroathenic symptoms and ICD-codes fitting the organic solvent syndrome, among the patients who worked the longest as painters. Instead, with respect to the ICD-codes no dose-effect relationship was detected and the highest prevalence of symptoms was found among the lowest exposed painter group. The reason for this last observation remains unclear, but certainly does not support the existence of a dose-effect relationship.

The items we chose for indicating the severity of the mental disorder were rather crude. It is noteworthy that they all occurred more often among the exposed group, but as a result of the lack of substantial significance no far reaching conclusion may be drawn from this observation.

All in all the results of our study are not in favour of the existence of any specific neurotoxic syndrome among neuropsychiatric patients with previous exposure to organic solvents. Probably exposure to organic solvents has a more general neurotoxic effect not distinguishable from other mental disorders by means of specific symptoms or syndromes. These results indicate that a broad variation of neuropsychiatric disorders should be included in studies designed to detect

any risks of solvent exposed workers to be prematurely disabled due to neuropsychiatric disorders.

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CHAPTER 5

NEUROPSYCHIATRIC DISORDERS AMONG SOLVENT EXPOSED WORKERS.
FIRST RESULTS FROM A DUTCH CASE-CONTROL STUDY.*

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ABSTRACT

This case-control study was undertaken to determine whether exposure to organic solvents, as experienced by Dutch painters, causes an increased risk for disability due to neuropsychiatric disorders. Cases and controls were selected from the Dutch Painters and Construction Workers Organizations.

Cases were defined as male persons receiving disability benefits due to neuropsychiatric disorders. The controls consisted of a random sample of 1,000 male persons from the total study population. 252 Cases and 822 controls participated in our study by returning the completed questionnaires. The questionnaire was used to collect information about their occupational history and the presence of potential confounding factors. The adjusted Odds Ratio for the total group of neuropsychiatric disorders did not reach a statistical significant level (OR = 1.17 $p < 0.30$). Although a stronger association was suggested between "neuroses" (ICD 300) and exposure to organic solvents (OR = 2.30; $p < 0.05$), there are indications that this relationship is merely the result of classification bias. The results of this study do not confirm, but do also not completely exclude, that Dutch painters are at increased risk for being prematurely disabled due to neuropsychiatric disorders.

INTRODUCTION

During the past fifteen years the question whether long-term exposure to organic solvents can induce chronic neurotoxic effects, has received quite some attention in the bio-medical literature¹. Epidemiological studies, particularly from Scandinavian countries, reported increases of disturbed psychological functions²⁻⁶, electroencephalographic abnormalities⁶⁻⁸ and an increased prevalence of neuroathenic symptoms^{3,6,8-10} among workers with long-term exposure to organic solvents.

The question was raised whether these chronic neurotoxic effects might lead to premature disability among solvent exposed workers. Four Scandinavian studies have investigated this issue. A Swedish and a Danish case-control study among construction workers who had been granted disability pensions showed an increased morbidity due to neuropsychiatric disorders among solvent exposed construction

workers^{11,12}. The results of a Finnish case-control study indicated that exposure to organic solvents was associated with an increased risk of being prematurely pensioned due to neuroses, while early pensioning due to other neuropsychiatric disorders was not increased among solvent exposed workers¹³. In a Danish cohort study painters had an increased risk to be pensioned due to presenile dementia¹⁴. Some studies conducted outside Scandinavia did not confirm these results. Cherry and Waldron¹⁵ found no evidence of an association between psychiatric morbidity and organic solvent exposure in British workers. Triebig et al¹⁶ concluded that German construction painters are not at increased risk for developing mental disorders.

Painters are usually exposed to a mixture of organic solvents. A study concerning the exposure of Dutch maintenance painters to organic solvents¹⁷ revealed exposure to C8-C11 alkenes and C7-C10 aromates among all painters while incidentally alcohols, ketones, esters and chlorated hydrocarbons were detected in the breathing zone. The hygienic standards of these solvents were rarely exceeded. However, the above mentioned measurements are not representative for the individual exposure to organic solvents of all painters. Furthermore, in the past thirty years considerable changes have occurred with regard to the nature and level of organic solvent exposure among Dutch painters¹⁸.

The present case-control study was undertaken to clarify some of the contradicting results obtained in Scandinavian studies compared to studies conducted outside Scandinavia and to determine whether exposure to organic solvents, as experienced by Dutch painters, is associated with the risk for receiving disability benefits due to neuropsychiatric disorders.

MATERIAL AND METHODS

In the study presented in this article a population based case-control design was applied. The first step at the start of a population based case-control study is to define the population from which cases and controls will be selected. The population base was taken from the Dutch Painters and Construction Workers Organizations. These organizations have been founded by employers and employees in order to execute a number of social laws, such as health care, unemployment and disability insurances for painters and construction workers. In The Netherlands the disability pension system has its legal basis in a specific disability act.

According to this act payment of disability benefits starts after 52 weeks of illness. Local departments of social security physicians engaged in granting of disability benefits cover the members of both organizations. Members of the above mentioned organizations, receiving disability benefits are centrally registered. If only the members of the painters organization were included in the study, nearly all cases and controls would have been more or less exposed to organic solvents. In order to include non-exposed persons in the study population, one fifth of the construction workers organization was incorporated into the study. A selection was made by including only those members of the construction workers organization in our study population, who were born on day no. 06, 07, 16, 17, 26, 27 of any month in any year. From this combined population of about 74,000 persons, as registered in July 1985, cases and controls were selected.

Cases were defined as male persons receiving disability benefits for mental disorders as from a date between 1 July 1984 and 1 July 1986. Diagnoses of persons receiving disability benefits for neuropsychiatric disorders were awarded by social security physicians. These diagnoses were coded by expert nosologists according to a classification based on the 9th revision of the International Classification of Diseases. Mental disorders are grouped in categories (Table 5) which have all been included in the study.

The controls consisted of a stratified random sample of 1,000 male persons (non-cases) from the total study population, taking into account the differences in population size and age distribution between the painters and construction workers organizations. The structure of the population base and the control population is presented in Table 1.

Cases and controls were approached by telephone in order to ask them to participate in this study. The study was restricted to persons who could be approached by telephone. In an early phase of the data collection it became clear that the response rate within the group without telephone turned out to be very low (about 20%). Furthermore, as shown in Table 2, there are no important differences between cases and controls with respect to telephone connections. Therefore the above mentioned restriction of the study population seems justifiable.

After cases and controls were approached by telephone and having consented to participate in the study, participants received a mailed questionnaire to collect information about their occupational history and the presence of potential confounding factors (e.g. alcohol intake, education level, stress factors). The willingness to participate in this study was somewhat higher among the controls.

Table 1: Age distribution of the population base and of the randomly selected stratified control sample of 1,000 persons.

Year of birth	SFS		SFB		Total	
	n	(%) Number of controls	n	(%) Number of controls	n	(%) Number of controls
1915-1919	0	(0.0) 0	4	(0.0) 0	4	(0.0) 0
1920-1924	217	(0.6) 3	334	(0.9) 5	551	(0.7) 8
1925-1929	693	(1.9) 9	1,344	(3.5) 18	2,037	(2.6) 27
1930-1934	1,734	(4.8) 23	2,470	(6.5) 33	4,204	(5.7) 56
1935-1939	2,345	(6.5) 32	3,467	(9.1) 47	5,812	(7.9) 79
1940-1944	3,340	(9.3) 45	4,475	(11.8) 61	7,815	(10.6) 106
1945-1949	5,521	(15.4) 75	6,180	(16.2) 83	11,701	(15.8) 158
1950-1954	6,073	(17.0) 82	5,939	(15.6) 80	12,012	(16.3) 162
1955-1959	6,115	(17.1) 83	5,791	(15.2) 78	11,906	(16.1) 161
1960-1964	6,828	(19.1) 93	5,511	(14.5) 75	12,339	(16.7) 168
1965-1969	2,945	(8.2) 40	2,564	(6.7) 35	5,509	(7.5) 75
Total	35,811	(100.0) 485	38,079	(100.0) 515	73,890	(100.0) 1,000

Table 2: Response among cases and controls.

	Painters Organization		Construction Workers Organization	
	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)
No telephone connection	58 (23.7)	100 (20.6)	38 (14.6)	78 (15.1)
Refusers	69 (28.2)	123 (25.4)	88 (33.8)	126 (24.5)
Participants	118 (48.2)	262 (54.0)	134 (51.5)	311 (60.4)
Total	245 (100.0)	485 (100.0)	260 (100.0)	515 (100.0)

In the analysis of the collected data Odds Ratios (OR) and confidence limits (two sided, $\alpha = 0.05$) were calculated according to Schlesselman¹⁹. The Odds Ratio

approximates the relative risk under the condition that the prevalence of the disease is low in both the exposed and the non-exposed group. Furthermore, the OR as such is a commonly used measure of the strength of the relationship between exposure and illness²⁰.

A logistic regression model was applied to adjust the Odds Ratios for potential confounding factors. Chi square test and Student's t-test were used to analyse the significance of the differences between cases and controls with respect to some population characteristics.

RESULTS

The questionnaire was returned by 252 cases and 822 controls. The number of controls differs from the figure in Table 2, as new controls were selected to compensate for the non-response group within this population. The refusal rate within this additional control group remained more or less the same. The number of cases was limited to 505 during the study period, therefore the same procedure could not be applied to the cases population. Table 3 shows some characteristics of the study population, based on information collected by the questionnaires.

As can be seen from this table, cases and controls differ significantly with respect to several factors. For all cases and controls (including refusers and non-approachable persons) it was known from which organization they originated. Probably most persons occupationally exposed to organic solvents were members of the painters organization, while most non-exposed persons originated from the construction workers organization. Table 4 shows a 2 x 2 Table, based on the assumptions that only members of the painters organization are exposed to organic solvents and all cases and controls (including refusers and non-approachable persons) participated in the study.

Furthermore, for all cases ICD-codes were available, whether or not they had participated in our study. This created the possibility to make a subdivision by type of neuropsychiatric disorder. Consequently, unadjusted Odds Ratios could be calculated for all cases and controls whether or not eventually participating in the study. Using this approach the results as shown in Table 5 were calculated.

Table 3: Characteristics of the study population.

	Cases		Controls	
	N	(%)	N	(%)
Mean age (years)	42.9		35.5*	
Divorced/widower	26	(10.3)	12	(1.5)*
Education level: 1 (low)	214	(84.9)	706	(85.9)
2 (medium)	32	(12.7)	103	(12.5)
3 (high)	6	(2.4)	13	(1.6)
Alcohol-intake: none	57	(22.6)	77	(9.4)*
< 25 consumptions/week	175	(69.4)	661	(80.4)*
≥ 25 consumptions/week	20	(7.9)	84	(10.2)
Smoking	211	(83.7)	626	(76.2)*
Positive family history of dementia	17	(6.7)	26	(3.2)*
Previous head trauma	43	(17.0)	88	(10.7)*
Other illnesses (diabetes, hypertension, cardiovascular dis., epilepsy, thyroid gland.)	82	(32.5)	97	(11.8)*
Private stress	117	(46.4)	100	(12.2)*
Work stress	56	(22.2)	27	(3.3)*

* $p < 0.05$ (χ^2 -test; Student's t-test)

Table 4: Relationship between neuropsychiatric disorders and organization membership, assuming that only members of the painters organization are exposed to organic solvents and all cases and controls participated in the study.

	Neuropsychiatric disorder		
	Yes	No	Total
Painters Organization (exposed)	245	485	730
Construction Workers Organization (non-exposed)	260	515	775
Total	505	1000	1505

OR = 1.00 (0.81 - 1.24)

Table 5: Odds Ratios of ICD-codes of all cases, including non-response and non-approachable group.

ICD-codes of mental disorders	Painters Organization (exposed)		Construction Workers Organization (non-exposed)		OR	Confidence limits ($\alpha = 0.05$)
	N	(%)	N	(%)		
290 Dementia	-	-	2 (0.8)	-	-	-
296 Affective psychosis	5 (2.0)		8 (3.0)		0.66	0.21- 2.03
298 Other non-organic psychosis	3 (1.2)		-	-	-	-
300 Neurotic disorders	76 (31.0)		48 (18.5)		1.68	1.14- 2.47
301 Personality disorders	8 (3.3)		6 (2.3)		1.42	0.49- 4.12
303 Alcohol dependence syndrome	9 (3.7)		10 (3.8)		0.96	0.39- 2.38
304 Drug dependence	4 (1.6)		2 (0.8)		2.12	0.39-11.60
306 Physiological malfunction arising from mental disorders	12 (5.0)		14 (5.4)		0.91	0.42- 1.98
307 Anorexia nervosa	1 (0.4)		-	-	-	-
309 Adjustment reaction	122 (49.8)		157 (60.4)		0.83	0.63- 1.09
310 Specific non-psychotic mental disorders following organic brain damage	-	-	1 (0.4)		-	-
311 Depressive disorder, not elsewhere classified	5 (2.0)		12 (4.6)		0.44	0.15- 1.26
ICD-codes fitting the symptoms reported by other investigators to be related to long-term organic solvent exposure (300 + 309 + 311)	203 (82.9)		217 (83.5)		0.93	0.74- 1.17
Total number of cases	245 (100.0)		260 (100.0)		1.00	0.81- 1.24
Total number of controls	485		515			

It appears that members of the painters organization are more often diagnosed with neurotic disorders (ICD 300). On the other hand some diagnoses (e.g. ICD 309: adjustment reactions) are more frequent among the construction workers population. Reviewing the relevant literature, persons suffering from syndromes reported by other investigators to be related to long-term organic solvent exposure will most likely be diagnosed as 300 (neurotic disorders), 309 (adjustment reactions) or 311 (depressive disorder, not elsewhere classified). A combination of these codes did not indicate an increased risk for possibly exposed persons to be disabled because of neuropsychiatric disorders.

Not all members of the painters organization are exposed to organic solvent (e.g. administrative personnel). On the other hand exposure to organic solvents is encountered in quite some occupations within the construction industry. A high degree of exposure will certainly be present among painters, carpet layers, paint sprayers and road markers. Although persons from other occupations may also be exposed to organic solvents, their exposure was considered to be of little significance compared to the occupations mentioned above. Consequently all persons who worked or had worked as painter, car sprayer, carpet layer or road marker (as stated in the questionnaire) were classified as exposed to organic solvents, while all other persons were classified as non-exposed.

Table 6 shows a 2 x 2 Table based on this classification.

Table 6: Relationship between neuropsychiatric disorders and exposure to organic solvents in our study population.

	Neuropsychiatric disorder		
	Yes	No	Total
Exposure to organic solvents: Yes	117	379	496
No	135	443	578
Total	252	822	1074

OR = 1.01 (0.76 - 1.34)

Here again Odds Ratios could be calculated for different types of neuropsychiatric disorders (Table 7).

Table 7: Odds Ratios of diagnostic codes of the participants.

ICD-codes of mental disorders	Exposed		Non-exposed		OR	Confidence limits ($\alpha = 0.05$)
	N	(%)	N	(%)		
296 Affective psychosis	5	(4.3)	2	(1.5)	2.92	0.56- 5.13
298 Other non-organic psychosis	1	(0.8)	-	-	-	-
300 Neurotic disorders	38	(32.5)	23	(17.0)	1.93	1.13- 3.30
301 Personality disorders	4	(3.4)	2	(1.5)	2.34	0.43-12.85
303 Alcohol dependence syndrome	4	(3.4)	5	(3.7)	0.94	0.25- 3.53
304 Drug dependence	2	(1.7)	0	(0.0)	-	-
306 Physiological malfunction arising from mental disorders	5	(4.3)	12	(8.9)	0.49	0.17- 1.40
307 Anorexia nervosa	1	(0.8)	-	-	-	-
309 Adjustment reaction	54	(46.2)	85	(63.0)	0.74	0.51- 1.07
310 Specific non-psychotic mental disorders following organic brain damage	-	-	1	(0.7)	-	-
311 Depressive disorder, not elsewhere classified	3	(2.6)	5	(3.7)	0.70	0.17- 2.95
ICD-codes fitting the symptoms reported by other investigators to be related to long-term organic solvent exposure (300, 309, 311)	95	(81.2)	113	(83.7)	0.98	0.72- 1.33
Total number of cases	117	(100.0)	135	(100.0)	1.01	0.76- 1.34
Total number of controls	379		443			

In general, Table 6 and Table 7 show the same results as appearing from Table 4 and 5. A combination of all ICD-codes does not indicate an increased risk for exposed persons to be disabled because of neuropsychiatric disorders, but the subdivision of neuropsychiatric disorders suggests an association between neuro-

tic disorders and exposure to organic solvents.

In order to adjust the OR for the influence of several confounding factors, a logistic regression analysis was conducted, including 6 variables (age, education level, marital status, alcohol intake, smoking and Quetelet-index). Other potential confounders (family history of dementia, head trauma, other diseases) did not change the OR. Inclusion of the variable "stress" in the logistic regression model decreased the OR. Apparently stress is very strongly associated with mental disorders. Because it can not be excluded that stress is rather a result than a cause of neuropsychiatric disorders, stress was finally not included in the logistic regression model. Table 8 shows the adjusted OR for several (groups of) ICD-codes.

Table 8: Odds Ratios for several (groups of) ICD-codes adjusted for differences in age, education level, marital status, smoking, alcohol consumption and Quetelet-index.

	Adjusted OR	Confidence limits ($\alpha = 0.05$)
ICD 300	2.30	1.19 - 4.08
ICD 309	0.86	0.57 - 1.29
ICD 300 + 309 + 311	1.16	0.82 - 1.63
All ICD-codes	1.17	0.85 - 1.61

As can be seen from this Table adjustment for confounding factors results in a slight increase of the Odds Ratios, without altering the trends as appearing from previous Tables.

DISCUSSION

This study was conducted in order to investigate whether Dutch painters compared to other construction workers are at increased risk for disability due to neuropsychiatric disorders. The results of this study do not confirm, but do also not exclude, the existence of such a risk among painters. While interpreting these

results it must be kept in mind that several potential sources of bias may have affected the results of this case-control study. In view of the existence of a large non-response group, a considerable amount of selection bias may have occurred. Yet, the similarity in results between Table 5 and Table 7 indicates that bias, perhaps introduced by selective non-response, did not essentially affect the results of our study. The classification of neuropsychiatric disorders by social security physician may be a source of potential classification bias. The physicians who grant benefits to insured disabled persons are no psychiatrists and diagnostic difficulties may easily arise in the field of neuropsychiatric disorders. For example, it is often difficult to distinguish between a "normal" and a "disproportionate" reaction to a distressing experience (ICD 309 vs. ICD 300). Therefore we can not rule out the possibility that the established relationship between exposure to organic solvents and neurotic disorders is merely the result of "misclassification" bias due to information bias. The results of a further analysis into this relationship are described in Chapter 7.

It is of interest to compare our results with the Scandinavian case-control studies investigating the same topic, i.e. the relationship between exposure to organic solvents and premature disability due to neuropsychiatric disorders. Axelson et al¹¹ and Olsen and Sabroe¹² detected an increased risk for all non-specific mental disorders, while Lindström et al¹³ could only demonstrate an increased risk among solvent exposed workers for developing neurotic disorders. Although the results of our study resembles Lindström's study, the strength of the association differs considerably (OR = 2.3 vs. OR = 5.5).

Various hypothesis can be postulated that may explain the differences in results between this study and the Scandinavian studies. First it must be noted that the disability pension systems for Scandinavian countries and The Netherlands are not identical, with as a possible result some kind of selection bias, which may be responsible for the contradictory results.

Secondly, the control group in the Scandinavian studies consisted of persons receiving disability benefits for reasons other than neuropsychiatric disorders. This choice has been criticized²¹. If some non-solvent occupations are more physically demanding, leading to more disability benefits for instance due to musculo-skeletal disorders, a relative underrepresentation of solvent exposed workers will occur in the control group. Consequently, the calculated OR will artificially increase. Although there were indications in the Scandinavian studies that disorders of the musculoskeletal system had been at least as common among painters as among construction workers, we clearly avoided this hypothetical pitfall by selecting healthy persons, receiving no disability benefits, as controls.

Thirdly in this study a case was defined as a person receiving benefits coded in the broad category of "neuropsychiatric disorders", while the Scandinavian epidemiologists used a more restrictive selection of ICD-codes. However, in view of the classification difficulties arising in this diagnostic area and the vague symptoms associated with long-term organic solvent exposure, it is difficult to decide which ICD-codes should be excluded from the study. Therefore it is not desirable to exclude a priori certain ICD-codes in this type of study design. Additional support for this view is derived from our study results. The statistically association between neurotic disorders and organic solvent exposure disappeared after a combination was made of various ICD-codes fitting the symptoms reported by other investigators to be related to long-term organic solvent exposure.

Finally, it is possible that Scandinavian painters really are more at risk for neuropsychiatric disorders than Dutch painters. At the moment quite some attention is paid in the Scandinavian countries to reduce the exposure of workers to organic solvents. However, it is possible that in the past exposure to organic solvents has been very high in these countries because of differences in working conditions.

An advantage of this study compared to most Scandinavian studies is the possibility to use more extensive information about several potential confounding factors, as collected by the questionnaires. To control confounding a logistic regression model was used. A remarkable observation concerns the drop of the OR after inclusion of "stress" in the model. It can not be ruled out that stress is the result, rather than the cause of the development of neuropsychiatric disorders. On the other hand we may hypothesize that exposure to organic solvents reduces the ability to cope with stress and thus leads to more disproportionate reactions to distressing experiences among solvent exposed workers. Consequently, this hypothesis could perhaps explain the relationship between organic solvent exposure and neuroses, as appearing from this study.

In spite of some improvements in our study design compared to the Scandinavian studies, we realize that still objections can be put forward against this study. Assessment of exposure to organic solvents was merely based on occupational history and no exact quantitative data on this exposure were available. At the moment an analysis is in progress to investigate dose-response relationships within our study population, using supplementary and more detailed information from the questionnaires of exposure to organic solvent of the participants. Results of this analysis are described in Chapter 6.

Furthermore, broad case definitions were used which included a variety of neuro-

psychiatric disorders. However, more restrictive case-definitions could be used in the analysis by calculating Odds Ratios for different (groups of) ICD-codes.

Notwithstanding the above mentioned shortcomings we conclude that our study results suggest that Dutch painters have no substantially increased risk for being prematurely disabled due to neuropsychiatric disorders. However, facing the fact that misclassification might have occurred both for exposure and diagnoses, the existence of a (small) increased risk among painter to be prematurely disabled due to neuropsychiatric disorders, especially with respect to neurotic disorders, can not be excluded. Furthermore, mild manifestations of organic solvent intoxication do perhaps not lead to prolonged disability and disability benefits. Therefore, the results of this study do not rule out the possibility of the existence of chronic neurotoxic effects, e.g. manifested by the occurrence of neurasthenic symptoms, due to exposure to organic solvents occurring in the painting industry. A further analysis of neurasthenic symptoms among workers exposed to organic solvents is presented in Chapter 8.

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CHAPTER 6

DOSE-RESPONSE RELATIONSHIPS BETWEEN ORGANIC SOLVENT EXPOSURE AND NEUROPSYCHIATRIC DISORDERS: RESULTS FROM A DUTCH CASE-CONTROL STUDY*

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ABSTRACT

In this article the material collected for a case-control study is analysed in order to evaluate the existence of dose-response relationships between organic solvent exposure and the entitlement to disability benefits due to neuropsychiatric disorders.

Questionnaires were used to collect information on 252 cases receiving compensation due to neuropsychiatric disorders and 822 controls about their occupational history and work practices related to organic solvent exposure. In order to estimate the exposure to organic solvents three exposure indices were used: duration of exposure, painters index and general exposure index. The analysis showed some tendencies indicating positive dose-response relationships. Furthermore some work practices and working conditions associated with high exposure to organic solvents (e.g. poor ventilation, using paint removers) resulted in a marked increase of the risk for receiving disability benefits due to neuropsychiatric disorders.

INTRODUCTION

Several studies indicating chronic neurotoxic effects due to long-term occupational exposure to organic solvents have been published since the early 1970s¹. In spite of this research, there is no international agreement about the nature and the classifications of disorders thought to be related to organic solvent exposure^{2,3}. Furthermore, still a number of other important questions remain unanswered. The underlying pathogenesis is unclear and requires further study^{3,4}. Another puzzling issue is the lack of consistent dose-response relationships in epidemiological studies investigating chronic neurotoxic effects of organic solvent exposure^{4,5}. If a risk factor is of causal importance in a disease, the risk of developing this disease should be related to the degree of exposure to this factor, that is, a dose-response relationship should exist⁶. Application of this axiom to long-term neurotoxic effects of organic solvent exposure brings to light conflicting results. The number of neurasthenic symptoms reported in solvent exposed workers was sometimes observed to be related to the degree of solvent exposure⁷⁻¹⁰, while other studies did not confirm such a relationship^{5,11-15}.

In neuropsychological tests, the performance of solvent exposed workers was generally not correlated with the duration or degree of solvent exposure^{5,10,12,14,16-18}. However, recent studies suggest a possible dose-response relationship between organic solvent exposure and intellectual impairment^{19,20}.

A number of case-control studies investigating the award of disability benefits due to mental disorders among solvent exposed workers documented varying results. Axelson et al²¹ and Olsen and Sabroe²² demonstrated indications of a dose-response relationship in terms of an increased risk for persons with longer or higher exposure to organic solvents. On the other hand, Lindström et al²³ could not demonstrate such a correlation. Finally, the general prognosis of Scandinavian workers, diagnosed as suffering from an "organic solvent syndrome", was not related to their former degree of solvent exposure^{17,24,25}.

More recently, various authors suggest that the development of an organic solvent syndrome may only occur after approximately ten years of solvent exposure or after repeated periods of acute intoxication^{9,26-28}.

From all of the above it is clear that uncertainty remains with regard to the existence of neurotoxic effects due to organic solvent exposure. Studies investigating dose-response relationships are hampered by the lack of exact qualitative or quantitative data on solvent exposure and the fact that most workers (e.g. painters) are exposed to a mixture of organic solvents.

Recently a case-control study in The Netherlands investigated whether Dutch painters were at increased risk of developing mental disorders. Overall no relationship was detected between organic solvent exposure and the risk of receiving disability benefits due to neuropsychiatric disorders. However, in that initial analysis exposure was merely defined as "present" or absent".

In this study more detailed information on exposure to organic solvents of the participants, as collected by questionnaires, is analysed in order to evaluate the existence of dose-response relationships between organic solvent exposure and neuropsychiatric disorders with disability benefits entitlement.

MATERIAL AND METHODS

The study material consisted of information from questionnaires as collected in a recently carried out case-control study. From the Dutch Painters and Construction Workers Organizations cases and controls have been selected. Cases were de-

defined as males awarded disability benefits due to neuropsychiatric disorders between 01-07-1984 and 01-07-1986. In The Netherlands payment of disability benefits is considered after 52 weeks of illness. Diagnoses of persons receiving disability benefits are made by social security physicians. These diagnoses were coded by expert nosologists according to a list based on the 9th Revision of the International Classification of Diseases. Mental disorders are grouped in categories, which have all been included in the study. Table 1 shows the ICD-codes of the cases included in our analysis.

Table 1: ICD-codes of cases included in the analysis of dose-response relationships.

ICD-codes	N	(%)
296 Affective psychosis	7	(2.8)
298 Other non-organic psychosis	1	(0.4)
300 Neurotic disorders	61	(24.2)
301 Personality disorders	6	(2.4)
303 Alcohol dependence syndrome	9	(3.6)
304 Drug dependence	2	(0.8)
306 Physiological malfunction arising from mental disorders	17	(6.7)
307 Special symptoms or syndromes not elsewhere classified	1	(0.4)
309 Adjustment reaction	139	(55.2)
310 Specific non-psychotic mental disorders following organic brain damage	1	(0.4)
311 Depressive disorder, not elsewhere classified	8	(3.2)
Total	252	(100.0)

The control population consisted of a random sample of males from the Dutch Painters and Construction Workers Organizations. Participants received a questionnaire that asked about their occupational history, health complaints and work practices related to organic solvent exposure. Potential confounding factors, such as alcohol intake, education level and stress factors were also examined. In order to estimate the exposure of the participants to organic solvents, three exposure indices were used:

1. The duration of exposure index.

Occupational exposure to organic solvents is encountered in many occupations

within the construction industry. A high degree of exposure exists for painters, carpet layers, paint sprayers and road markers. The number of years worked in one of the above mentioned occupations determined this index.

2. Painters index.

The exposure to organic solvents of an individual painter will depend on his work activities and working conditions. Some work activities, such as paint spraying, using alkyd paints and paint removers, lead to high exposure to organic solvents²⁹. Respondents were asked to indicate on a four point scale how often they were involved in the above mentioned painting practices. Furthermore a division was made between current and past situations. The scores for each item (1,2,3 or 4) were added up, attributing equal weights to the answers concerning the past and the current situation, to create the value of the painters index. Higher values of this exposure index were thought to indicate higher levels of exposure to organic solvents.

3. General exposure index.

As mentioned, exposure to organic solvent is not restricted to painters, carpet layers and road markers. Therefore all respondents were asked about the use of paint removers, organic solvents, glues and degreasing agents (i.e. substances probably containing organic solvents). Further, it was asked whether they had worked in one room with painters or carpet layers, hence being simultaneously exposed to organic solvents. Here again a division was made between the current and the past situations. Questions were scored and summed in the same way as the painters index. The total score was thought to be indicative for the exposure to organic solvents of each worker, whether or not he was directly involved in painting activities.

In addition to the exposure indices, information was collected about several other work practices and working conditions of painters. The exposure indices and additional information about painting activities were used to define the "dose" of organic solvent exposure, while the "response" was defined as neuropsychiatric disorders with disability entitlement.

To describe the dose-response relationships mathematical equations were drawn up using logistic regression analysis. Correction for six potential confounding factors (age, education level, marital status, alcohol intake, smoking and Quetelet-index) was performed by using the same technique. Odds ratios (OR) and confidence limits were calculated according to Schlesselman³⁰. The OR is a common measurement of the strength of the relationship between exposure and illness.

RESULTS

There were 252 cases (response: 61.6%) and 822 controls (response: 69.7%) who participated in our study by returning completed questionnaires. 46.4% Of the cases and 46.1% of the controls had or had ever worked as a painter, carpet layer or road marker. The mean exposure duration was 20.6 (SD 11.6) years for the cases and 15.6 (SD 10.7) years for the controls. Dose-response relationships were analysed and correction for confounders was performed by applying logistic regression techniques. The results of this analysis are graphically represented by relating each value of the exposure index under study to the corresponding estimated value of the OR.

Figure A: Dose-response relationship between duration of exposure (years worked as painter, carpet layer or road marker) and the risk for receiving disability benefits due to neuropsychiatric disorders.

Figure B: Dose-response relationship between the painters index and the risk for receiving disability benefits due to neuropsychiatric disorders.

Figure A shows the dose-response relationship for duration of exposure. There is only a small increase of the OR as the duration of exposure increases. This relationship is not statistically significant ($p < 0.60$). An analysis for four different groups of painters (new building, maintenance, construction and "other" painters) revealed no positive dose-response relationship regarding duration of exposure. The relationship between the painters index and the Odds Ratio is graphically represented in Figure B. In this case a higher value of the exposure index is accompanied by a steady increase in the OR, indicating a positive dose-response relationship ($p \leq 0.05$).

Figure C: Dose-response relationship between the general exposure index and the risk for receiving disability benefits due to neuropsychiatric disorders.

Figure D: Dose-response relationship of the general exposure index, separately analysed for painters (o) and construction workers (●).

Figure C shows the dose-response relationship for the general exposure index. Although this curve also demonstrates a positive trend, the statistical significance of this dose-response relationship is of a lower level ($p < 0.08$). This general exposure index was calculated for all study subjects, whether or not they had been working in one of the above defined solvent exposed occupations.

The relationship between the general exposure index and neuropsychiatric disorders with disability benefits entitlement was separately analysed for painters and for construction workers. The results are shown in Figure D. It appears from this analysis that the strength of the dose-response relationship among the painters is increased ($p < 0.05$), while the relationship in the construction workers is considerably weaker ($p < 0.70$), compared with the results of the combined analysis (Figure C).

Table 2 shows the frequency distribution of the painters index and the general exposure index, indicating that high values of these exposure indices are only present among a small group of painters and construction workers.

Table 2: Frequency distribution of the painters index and the general exposure index.

Painters index (N = 496)	n	(%)	General exposure index (N = 1074)	n	(%)
0 - 8	203	(40.9)	0 - 20	629	(58.6)
9 - 16	281	(56.7)	21 - 30	377	(35.1)
17 - 24	12	(2.4)	31 - 40	58	(5.4)
			41 - 48	10	(0.9)

As described in "Material and Methods", the painters index was based on information of the participants about their involvement in work practices with high solvent exposure. However, the choice of the painters activities included in this index was rather crude. Other factors, e.g. the use of respirators and the workplace ventilation, shall also influence the exposure of workers to organic solvents.

Furthermore, other chemical exposures, e.g. lead, associated with other painting activities are associated with chronic neurotoxic effects. On the other hand it is of interest to examine which components of the painters index contributed most to the positive trend of this dose-response relationship.

Table 3: Odds Ratios of painters activities compared to the non-exposed group, adjusted for differences in age, education level, marital status, smoking, alcohol consumption and Quetelet-index.

		"at present"		"earlier"	
		OR	(Confidence limits, $\alpha = 0.05$)	OR	(Confidence limits, $\alpha = 0.05$)
Latex paints	≤ 1 day/week	0.97	(0.67 - 1.41)	0.95	(0.64 - 1.38)
	> 1 day/week	1.68	(1.10 - 2.58)	1.80	(1.19 - 2.73)
Alkyd paints	≤ 1 day/week	1.29	(0.89 - 1.88)	1.18	(0.81 - 1.72)
	> 1 day/week	1.08	(0.71 - 1.64)	1.30	(0.85 - 1.98)
Epoxy paints	≤ 1 day/week	1.17	(0.84 - 1.64)	1.15	(0.82 - 1.60)
	> 1 day/week	1.36	(0.70 - 2.64)	1.77	(0.96 - 3.28)
"Other" paints	≤ 1 day/week	1.12	(0.79 - 1.58)	1.04	(0.73 - 1.48)
	> 1 day/week	1.47	(0.88 - 2.43)	1.91	(1.17 - 3.11)
Paint brushing	≤ 1 day/week	2.77	(1.47 - 5.22)	2.12	(1.03 - 4.32)
	> 1 day/week	1.04	(0.74 - 1.45)	1.15	(0.82 - 1.59)
Paint rolling	≤ 1 day/week	0.94	(0.65 - 1.38)	1.06	(0.74 - 1.51)
	> 1 day/week	1.69	(1.11 - 2.56)	1.70	(1.08 - 2.68)
Paint spraying	≤ 1 day/week	1.16	(0.84 - 1.61)	1.10	(0.79 - 1.54)
	> 1 day/week	1.65	(0.75 - 3.59)	2.56	(1.32 - 4.94)
Scouring off paints	≤ 1 x / week	1.32	(0.86 - 2.03)	1.14	(0.71 - 1.84)
	> 1 x / week	1.12	(0.78 - 1.63)	1.27	(0.89 - 1.80)
Burning off paints	≤ 1 x / week	1.03	(0.73 - 1.47)	0.89	(0.60 - 1.31)
	> 1 x / week	1.73	(1.08 - 2.77)	1.88	(1.25 - 2.83)
Paint removers	≤ 1 x / week	1.08	(0.77 - 1.52)	0.93	(0.65 - 1.34)
	> 1 x / week	1.87	(1.07 - 3.29)	2.22	(1.41 - 3.51)
Respirators	≤ 1 x / week	1.16	(0.84 - 1.62)	1.25	(0.89 - 1.74)
	> 1 x / week	1.42	(0.74 - 2.73)	1.08	(0.52 - 2.24)
Rooms	Poorly ventilated	2.21	(1.47 - 3.32)	6.54	(3.28 - 13.03)
	Well ventilated	0.73	(0.42 - 1.63)	1.70	(0.59 - 4.89)
	Outdoors	0.79	(0.51 - 1.21)	1.02	(0.45 - 2.31)

Therefore, information about these exposures, as collected by the questionnaires, was separately analysed. Odds Ratios were calculated for the relevant working conditions and work practices. In this case the OR reflects the risk for receiving disability benefits due to neuropsychiatric disorders in a certain exposure group compared with this risk in the non-exposed group. As can be seen from Table 3, the OR is considerably increased for several work practices of painters. The highest values of the Odds Ratio are found for sporadic paint brushing, frequent spray painting, frequent use of paint removers, frequently burning off paints and working in poorly ventilated rooms.

DISCUSSION

The quantification of exposure to organic solvents is one of the difficulties encountered in conducting retrospective epidemiological studies to investigate chronic neurotoxic effects of occupational solvent exposure. Usually no exact exposure data are available and the amount of solvent exposure must be estimated using information from company records or questionnaires. However, there is substantial variation between individual painters regarding work practices and working conditions, which may affect individual solvent exposure. In this study three indices were used to define the exposure to organic solvents: duration of exposure (years), painters index and general exposure index. The exposure indices used in this study can be criticized because the questionnaire design does not permit an accurate estimate of the exposure to organic solvents.

Bias may have influenced our results. Painters with neuropsychiatric disorders tend to blame their work and might therefore indicate more unfavourable work conditions. Recently Fidler et al¹⁰ proposed the use of a more sophisticated exposure index based on information about the total number of gallons of paint used per year, the fraction which would be absorbed by a respirator, the method of application and the presence of ventilation. Although this exposure index might prove to be a useful tool for epidemiological investigations, one has to be aware of the danger to introduce an overestimation of the accuracy of the data collected by means of questionnaires or interviews. For instance, these data are very sensitive to information bias.

Relationships were investigated between the height of the exposure indices and the risk for receiving disability benefits due to mental disorders. The duration of exposure did not show a dose-response relationship. Duration of exposure is a common surrogate estimation of exposure dose for investigating dose-response relationships^{11,16,17,22,31,32}. However, use of this exposure index has been criticized, since it ignores the intensity and type of organic solvent exposure¹⁰. Furthermore, the strong correlation between age and duration of exposures makes it difficult to distinguish solvent effects from the effects of aging¹⁰. Although in our study, age was taken into account as a potential confounding factor, still no dose-response relationship could be detected.

The painters index seemed to be positively associated with the risk for neuropsychiatric disorders. However, high values of this painters index are only present among a small group of painters. A subdivision of this index into the work practices which were included in this index revealed paint spraying and paint removing as potentially important risk factors. Paint removers contain up to 90% organic solvents, usually methylene chloride. A strong retardation of the evaporation of methylene chloride is effectuated by adding solid paraffin to paint removers. Solid paraffin forms a layer above the applied paint remover, thus retarding evaporation of methylene chloride and promoting the effectivity of the paint remover. However, after scraping off the paint remover containing paint layers, almost all of the methylene chloride will evaporate, leading to high exposure of the involved workers. Studies of workers exposed to methylene chloride showed an excess of self-reported neurological symptoms, although no evidence was found of long-term neuropsychological damage³³. The analysis of dose-response relationships with respect to the general exposure index showed some interesting results. It became evident that for each value of this exposure index, painters were more at risk than construction workers.

Various explanations can be put forward in order to explain this difference. First it is possible to assume that at the same level of this index painters are more exposed than construction workers. This exposure index is based on questions about the number of days per week involved in work practices with organic solvent exposure. It is likely that painters indicating the use of organic solvents during five days per week are exposed all day, while non-painters giving the same answers are only exposed during short periods, e.g. cleaning activities. On the other hand, we can not rule out the possibility that this difference between painters and construction workers indicates the importance of factors other than solvent exposure, that may increase the risk for painters to develop neuropsychiatric disorders. Supplementary evidence for this hypothesis might be deri-

ved from the list of painters activities which were associated with an increased OR. Some factors are clearly associated with high exposure to organic solvents, for example working in badly ventilated rooms. Riala et al³⁴ noted that good ventilation could reduce the exposure to organic solvents as much as 80 percent. However, this possible translation to high organic solvent exposure can not be made for other factors such as using "other paints" or "burning off paints". Of course "other paints" is a very vague term and gives no indication about the solvent concentration of the paints used by the participants who answered positively on this item. However, some participants indicated the use of lead containing paints ("lead white"). In the past, lead exposure has been an important health hazard for painters and lead intoxication is accompanied by neurological and neuropsychiatric symptoms and signs³⁵. The amounts of leads used in painting are now largely reduced, yet exposure to lead can occur while burning off old paint coatings³⁶.

At first sight, some of the results of the analysis of different painting activities are rather curious; in particular the high OR for paint brushing and using latex can not easily be explained. However, it has to be remembered that the statistical analysis of our data limits the interpretation of the results, since the mutual relation between the various painting activities is not taken into account. In view of the great variety of painting activities and the limited number of observations, such an analysis would not produce reliable results. It might be reasonable to assume (and confirmed by simple analysis) that painters with little involvement in brushing activities are more active in paint rolling and paint spraying, hence having higher exposure to organic solvents than painters doing mainly paint brushing. Moreover, our data showed that painters with frequent use of latex paints also use more paint removers, thus having high exposure to methylene chloride. Nevertheless, it is unclear whether these explanations totally account for the detected increase of the OR.

In this study, much attention was given to the question how to define the dose of organic solvent exposure. Of course it is of equal importance to pay attention to the validity and reliability of the studied "response". Our study focussed on neuropsychiatric disorders with disability benefits entitlement, thus implying that disability due to neuropsychiatric disorders has been chosen as a parameter of the occurrence of neuropsychiatric disorders. However, disability is the result of a process involving both medical and social determinants. The relatively great extent of the disability figures in The Netherlands (in 1986 about 94,000 persons received disability benefits from the Dutch painters and construction workers organizations) supports the existence of social determinants in this

process, such as the situation on the labour market. Older people, experiencing difficulties in getting new jobs, might be put (wrongly) in disability categories. These factors introduce the possibility that some dilution of any existing dose-response relationship might have occurred. Furthermore, social security physicians granting these disability benefits are not psychiatrists and diagnostic difficulties may easily arise in the field of neuropsychiatric disorders, thus introducing the possibility of classification bias. However, all these potential sources of bias would have affected both painters and construction workers in the same way, since they are covered by one medical department.

On the whole, the following conclusions may be drawn from our study results. The analysis showed some tendencies indicating positive dose-response relationships between organic solvent exposure and neuropsychiatric disorders. Furthermore, some work practices and working conditions resulting in high exposure to organic solvents (using paint removers, working in poorly ventilated rooms) were associated with a marked increase of the OR. Thus, our study results suggest that a small group of painters with high exposure to organic solvents might have an increased risk to be prematurely disabled due to neuropsychiatric disorders. On the other hand, our data suggest that other chemical exposures, perhaps to lead, may also play a role in the development of neuropsychiatric disorders among painters.

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CHAPTER 7

NEUROTIC DISORDERS DUE TO ORGANIC SOLVENT EXPOSURE: FACT OR PITFALL?*

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ABSTRACT

The results of a Dutch case-control study revealed a relationship between organic solvent exposure and premature disability due to neurotic disorders. In order to evaluate the causal character of this relationship, an additional analysis was carried out of symptoms and exposure factors, as reported by persons receiving disability benefits due to neuropsychiatric disorders.

No significant differences were detected between persons diagnosed as having neurotic disorders and persons diagnosed as having other neuropsychiatric disorders with respect to the reported symptoms and exposure factors. It is concluded that this study does not support the existence of a causal relationship between organic solvent exposure and neurotic disorders. Consequently it can not be excluded that classification bias is responsible for the detected association.

INTRODUCTION

During the past fifteen years an intensive search has been carried out into the chronic neurotoxic effects of long-term exposure to organic solvents^{1,2}. The practical consequences of these neurotoxic effects have been studied in several Scandinavian studies, investigating the relationship between organic solvent exposure and premature disability due to neuropsychiatric disorders³⁻⁶. The results of these studies suggested that solvent exposed workers are at increased risk for being prematurely disabled due to neuropsychiatric disorders. Recently, a Dutch case-control study was carried out among Dutch painters and construction workers, investigating the same relationship. This study revealed a statistically significant association between organic solvent exposure and premature disability due to neurotic disorders, while such an association was not detected with respect to other neuropsychiatric disorders. These findings are in accordance with the results of Lindström et al⁶. The objective of the present study is to further examine and evaluate the causal character of the relationship between organic solvent exposure and neurotic disorders.

MATERIAL AND METHODS

The study material consisted of information from questionnaires as collected in a recently carried out case-control study. All cases and controls were affiliated to the Dutch Painters and Construction Workers Organizations. Cases were defined as male persons receiving disability benefits as from a date between 01-07-1984 and 01-07-1986. In The Netherlands payment of disability benefits is considered after 52 weeks of illness. Diagnoses of persons receiving disability benefits are awarded by social security physicians. These diagnoses are coded by expert nosologists according to a list based on the 9th revision of the International Classification of Diseases. The control population consisted of a random sample of male persons from the Dutch Painters and Construction Workers Organizations. From all participating cases and controls completed questionnaires were received. These questionnaires contained information about their occupational history, working conditions and work practices related to organic solvent exposure and the occurrence of neurasthenic symptoms. In accordance with the objective of our present study we further analysed the information collected from the cases group of our study.

In the analyses of the collected data Odds Ratios (OR) and Confidence Limits (two sided, $\alpha = 0.05$) were calculated according to Schlesselman⁷. Student's t-test was used to analyse the significance of the difference between the compared groups with respect to duration of exposure (years).

RESULTS

252 Persons receiving disability benefits due to neuropsychiatric disorders (response: 61.6%) and 822 controls (response: 69.7%) participated in our study. Table 1 shows the distribution of organic solvent exposure and neuropsychiatric disorders within the cases group. This table clearly indicates the association between organic solvent exposure and neurotic disorders (OR = 1.93). However, this association disappears as persons diagnosed with adjustment reactions are added to this group (OR = 1.00). Further analysis was carried out among the exposed cases group (n = 117). Persons diagnosed as having a neurotic disorder (n = 38) were compared to persons diagnosed as having other neuropsychiatric disorders (n = 79) with respect to several relevant symptoms and exposure factors.

Table 1: Distribution of exposure to organic solvent and ICD-codes within the cases group.

ICD-codes of mental disorders	Exposed		Non-exposed		OR ¹	Confidence limits ($\alpha = 0.05$)
	N	(%)	N	(%)		
300: neurotic disorders	38	(32.5)	23	(17.0)	1.93	1.13-3.30
309: adjustment reactions	54	(46.2)	85	(63.0)	0.74	0.51-1.07
Other ICD-codes with respect to neuropsychiatric disorders	25	(21.4)	27	(20.0)	1.08	0.62-1.89
300 + 309	92	(78.6)	108	(80.0)	1.00	0.74-1.36
Total	117	(100.0)	135	(100.0)	1.01	0.76-1.34

¹ Odds Ratios were calculated based on the participation of 379 exposed and 443 non-exposed controls in our study.

The questionnaire contained a list of 33 questions about the occurrence of neuroasthenic symptoms. Participants were asked to describe the situation as experienced during the last year. Answers had to be selected from four categories: never, sometimes (e.g. once a month), regular (e.g. once a week) or often (more than once a week). Persons included in Table 2 scored regular or often on the particular question.

As can be seen from this table none of the symptoms revealed a statistically significant difference between cases diagnosed with neurotic disorders and cases diagnosed with other neuropsychiatric disorders.

The symptoms listed in Table 2 may be grouped into 8 categories. The scores (1, 2, 3 or 4) on every question within a symptom group were summarized. Persons included in Table 3 scored above 50% of the maximum score (= number of symptoms times four) of the relevant symptom group.

Table 3 shows that this approach reveals no statistically significant differences between the compared cases groups.

The exposure of the individual painter to organic solvents will depend on his working conditions and work practices. Some of these factors, such as paint spraying, using alkyd paints or paint removers and working in poorly ventilated rooms, may lead to high exposure to organic solvents.

Table 2: Responses concerning neurasthenic symptoms associated with long-term organic solvent intoxication among exposed persons diagnosed with neurotic disorders (ICD-300) or other neuropsychiatric disorders.

	ICD-300 (n = 38)	Other neuro- psychiatric disorders (n = 79)	OR	Confidence Limits ($\alpha = 0.05$)
1. Do you get up tired in the morning?	21	50	0.72	0.33 - 1.58
2. Do you feel excess tiredness after the workday?	20	41	1.02	0.47 - 2.21
3. Are you forgetful?	12	30	0.75	0.33 - 1.70
4. Do you often forget what you intended to do?	10	29	0.62	0.26 - 1.48
5. Do you have to go back and check whether you turned off the gas, locked the door etc.?	11	33	0.57	0.25 - 1.31
6. Do you make notes of things you must remember?	14	24	1.34	0.31 - 1.60
7. Have your relatives or friends told you that you are forgetful?	3	17	0.31	0.08 - 1.13
8. Do your thoughts stray when you try to concentrate?	17	40	0.79	0.36 - 1.72
9. Do you fall asleep when watching television?	10	27	0.69	0.29 - 1.63
10. Are you lost in your own thoughts?	25	48	1.24	0.55 - 2.78
11. Do you notice that you are "daydreaming"?	10	23	0.87	0.36 - 2.08
12. Do you have difficulties understanding what you read in newspapers or books?	6	19	0.59	0.21 - 2.56
13. Do you have difficulties falling asleep?	16	34	0.96	0.44 - 2.10
14. Do you wake at night?	14	31	0.90	0.40 - 2.00
15. Do you have nightmares?	5	14	0.70	0.23 - 2.11
16. Does your mood change without reason?	8	30	0.44	0.18 - 1.09

Table 2 continued

	ICD-300 (n = 38)	Other neuro- psychiatric disorders (n = 79)	OR	Confidence Limits ($\alpha = 0.05$)
17. Are you depressed?	12	38	0.50	0.22 - 1.13
18. Are you irritated?	14	31	0.90	0.40 - 2.00
19. Are you restless?	23	46	1.10	0.50 - 2.42
20. Are you afraid?	13	26	1.06	0.47 - 2.40
21. Are you listless?	13	32	0.76	0.33 - 1.74
22. Are you drowsy?	10	25	0.77	0.32 - 1.83
23. Do you become tired among other people?	14	23	1.42	0.63 - 3.22
24. Do you have difficul- ties in starting a con- versation with others?	10	20	1.05	0.43 - 2.58
25. Do you suffer from headaches?	11	31	0.63	0.27 - 1.45
26. Do you suffer from dizziness?	6	23	0.45	0.17 - 1.22
27. Do you sweat without exerting yourself?	15	29	1.12	0.51 - 2.48
28. Do you have palpita- tions without exerting yourself?	8	12	1.49	0.55 - 4.02
29. Do your hands tremble?	11	22	1.05	0.45 - 2.47
30. Do you feel as though you have something in your throat?	7	17	0.82	0.31 - 2.19
31. Do you feel an oppres- sion on your chest?	11	22	1.05	0.45 - 2.47
32. Do you suffer from a diminished sexual interest?	11	27	0.78	0.34 - 1.81
33. Do your legs feel numb or tingle?	10	24	0.82	0.34 - 1.95

Table 3: Symptom groups: number of persons diagnosed with neurotic disorders (ICD-300) or other neuropsychiatric disorders scoring more than 50% of the maximum summarized group score.

Symptom groups	ICD-300 (n = 38)	Other neuro- psychiatric disorders (n = 79)	OR	Confidence Limits ($\alpha = 0.05$)
Fatigue (1 - 2)*	23	52	0.80	0.36 - 1.78
Forgetfulness (3 - 7)	15	44	0.52	0.24 - 1.14
Concentration difficulties (8 - 12)	22	47	0.94	0.43 - 2.06
Sleeping difficulties (13 - 15)	16	36	0.87	0.40 - 1.90
Lability of mood (16 - 24)	20	48	0.72	0.33 - 1.57
Headache and dizziness (25 - 26)	12	37	0.52	0.23 - 1.17
Vegetative symptoms (27 - 32)	15	35	0.82	0.37 - 1.80
Neuropathy (33)	10	24	0.82	0.34 - 1.95

* Numbers refer to the symptoms as listed in Table 2, that are included in the relevant symptom groups.

Table 4 shows the number of exposed persons diagnosed with neurotic disorders or "other neuropsychiatric disorders", who are frequently (more than one day per week) involved in the above mentioned workpractices and working conditions. Here again the comparison between the two groups of cases revealed no statistically significant differences.

In addition, the number of years worked as a painter is a commonly used, although not very accurate measure of exposure.

The mean exposure duration of cases diagnosed with neurotic disorders was longer (22.8 years) than the mean exposure duration of cases diagnosed with other neuropsychiatric disorders (19.6 years). However, this difference did not reach a statistically significant level (Student's t-test: $p = 0.17$).

Table 4: Painters activities associated with high exposure to organic solvents: a comparison of the scores from persons diagnosed with neurotic disorders (ICD-300) and persons diagnosed with other neuropsychiatric disorders.

	ICD-300 (n = 38)	Other neuro- psychiatric disorders (n = 78)*	OR	Confidence Limits ($\alpha = 0.05$)
	n (%)	n (%)		
Working at present (last working year) with/in:				
- Alkyd paints (> 1 day/week)	4 (10.5)	11 (14.1)	0.72	0.21 - 2.43
- Paint spraying (> 1 day/week)	3 (7.9)	9 (11.5)	0.66	0.17 - 2.59
- Paint removers (> 1 day/week)	3 (7.9)	10 (12.8)	0.58	0.15 - 2.24
- Poorly ventilated rooms	24 (63.2)	41 (51.9)	1.55	0.70 - 3.34
Working earlier with/in:				
- Alkyd paints (> 1 day/week)	16 (42.1)	31 (39.7)	1.10	0.50 - 2.42
- Paint spraying (> 1 day/week)	5 (13.2)	13 (16.7)	0.76	0.25 - 2.31
- Paint removers (> 1 day/week)	14 (36.8)	32 (41.0)	0.84	0.38 - 1.87
- Poorly ventilated rooms	24 (63.2)	39 (50.0)	1.71	0.77 - 3.79

* One person from the exposed cases group had worked as a carpet layer. Subsequently 118 cases (in stead of 119) were incorporated in this analysis.

DISCUSSION

The results of a recently carried out Dutch case-control study revealed a statistically significant relationship between organic solvent exposure and premature disability due to neurotic disorders. Several hypothesis can be put forward in order to explain this relationship. Possibly persons predisposed to develop neuropsychiatric disorders are more likely to choose occupations involving exposure to organic solvents^{4,5}. However, it is also possible that exposure to organic solvents impairs the ability of the involved workers to cope with stress, thus leading to disproportionate ("neurotic") reactions to distressing experiences. Of course, diagnostic difficulties may easily arise in the field of neuropsychiatric disorders. In particular, the distinction between neurotic disorders and adjustment reactions may be difficult. Whether a reaction to a distressing experience is judged as more or less normal ("adjustment reaction") or disproportionate ("neurotic") depends on a lot of factors, partly linked up with the frame of reference of the physicians involved in this judgement. In view of this diagnostic difficulties we hypothesized that classification bias was responsible for the detected association between organic solvent exposure and neurotic disorders. The effect of random misclassification would be to underestimate the true association between organic solvent exposure and neurotic disorders⁸. Hence hypothesizing that misclassification bias has lead to an overestimation of the Odds Ratio, implies that selective misclassification with respect to neurotic disorders must have occurred.

Yet, exposed and non-exposed persons applying for disability benefits were examined and diagnosed by social security physicians from the same medical departments, diminishing the probability of the occurrence of selective misclassification. An explanation could be that social security physicians hold some sort of prejudice against painters, leading to an inclination to diagnose their neuropsychiatric disorders as neurotic. It is also possible that knowledge of the relationship between organic solvent exposure and neuropsychiatric disorders leads to an "overdiagnosing" of neurotic disorders among painters. However, it is not clear why painters should be diagnosed as suffering from neurotic disorders (ICD-300) in stead of suffering from adjustment reactions (ICD-309). In fact, the decreased risk for painters to receive disability benefits due to adjustment reactions (OR = 0,86), whereas the combination of neurotic disorders (ICD-300) and adjustment reactions (ICD-309) shows no relationship with organic solvent exposure is a rather puzzling issue. Misclassification among painters towards

neurotic disorders and (reversed) among construction workers towards adjustment reactions is a possible explanation of our study results that can not be excluded nor confirmed. Yet the existence of classification bias can not be proved by these considerations, nor by any additional analysis of our studymaterial. However, it is possible to further investigate the relationship between neuroses and organic solvent exposure. This investigation was carried out by analysing information about symptoms and organic solvent exposure of persons diagnosed with neuropsychiatric disorders, as collected by questionnaires.

Complaints and symptoms reported by patients play an important part in the diagnostic proces of neuropsychiatric disorders, the more so as these disorders are usually not accompanied by objective physical signs. If there is a causal relationship between neurotic disorders and organic solvent exposure the symptoms reported by persons diagnosed as having a neurotic disorder ought to be more or less in line with the symptoms associated with chronic neurotoxic effects due to long-term organic solvent exposure².

Unfortunately, a comparison of the occurrence of these (neurasthenic) symptoms among persons diagnosed as having a neurotic disorder and persons diagnosed as having other neuropsychiatric disorders did not reveal statistically significant differences between these two groups. In fact, 22 out of 33 neurasthenic symptoms (66.7%) indicated a weak association with non-neurotic disorders, as the calculated Odds Ratio is lower than one. Furthermore, none of the symptom groups showed an association with neurotic disorders.

The existence of a causal relationship between the development of neurotic disorders among painters and their exposure to organic solvents would be supported if their occupational history indicated higher levels or longer exposure to organic solvents than the occupational history of painters diagnosed with other neuropsychiatric disorders. Therefore, we compared the occurrence of some painters activities associated with high exposure to organic solvents between these two groups. With regard to the factors used in this analysis no significant differences were found.

Critical observation might be added with respect to this analysis. First of all the small numbers of the compared groups certainly limitates the interpretation of the results. Consequently, significant differences can only be expected in case of very large differences between the compared groups with respect to for instance, the occurrence of neurasthenic symptoms. Furthermore, it is questionable whether the information about the relevant working conditions, as collected by questionnaires, actually reflects high levels of organic solvent exposure.

In spite of these shortcomings we may conclude that further analysis of our

study material certainly does not support the existence of a causal relationship between neurotic disorders and organic solvent exposure. Furthermore, the lack of difference between the symptoms reported by the compared groups indicates the existence of an overlap with regard to the symptoms associated with neurotic disorders and other neuropsychiatric disorders.

Consequently this study is not in contradiction with our hypothesis that classification bias is responsible for the, at first sight, statistically significant relationship between neurotic disorders and organic solvent exposure.

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CHAPTER 8

PRENARCOTIC AND NEURASTHENIC SYMPTOMS AMONG DUTCH WORKERS EXPOSED TO ORGANIC SOLVENTS.*

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ABSTRACT

In this study a population of Dutch organic solvent exposed workers (n = 379) was compared with a non-exposed population (n = 443) with regard to the prevalence of prenarctic and neurasthenic symptoms. Participants completed a questionnaire to collect information about their occupational history, exposure to organic solvents and the occurrence of symptoms. The results of this study indicated that solvent exposed workers have a higher reporting rate of prenarctic symptoms than workers not exposed to solvents. However, the prevalence of chronic neurotoxic effects, in the form of neurasthenic symptoms, was only weakly associated with reported exposure to organic solvents. The influence of workstress in the development of these symptoms is perhaps more important than the role of organic solvent exposure. It is concluded that the organic solvent syndrome type I, as defined by an international working group, is not an important health hazard among Dutch painters.

INTRODUCTION

Exposure to organic solvents frequently occurs in various types of industries and constitutes a potential health hazard to millions of workers throughout the world¹. Before the 1970s some knowledge existed of the acute (narcotic) effects of various organic solvents on the central nervous system (CNS), but little attention was given to the possible chronic effects of long-term exposure to relatively low concentrations of organic solvents². However, this situation has significantly changed over the past fifteen years. Several studies have reported adverse effects on the central nervous system among workers with long-term exposure to organic solvents^{3,4}. Despite these findings there is still no international agreement about the classification and categorization of the chronic neurotoxic effects supposed to be induced by long-term organic solvent exposure^{5,6}. One of the most consistent findings in studies investigating these chronic neurotoxic effects is an increase in the number of reported neurasthenic symptoms, such as concentration difficulties, emotional lability and sleep disturbances among solvent exposed workers. It is proposed that symptom questionnaires are a useful tool for screening workers who may be at higher risk to be effected by

exposure to organic solvents^{2,7}. Workers with high scores should be further examined by specially trained physicians.

One of the difficulties encountered in constructing these questionnaires was the existing overlap between the symptoms of acute organic solvent intoxication (prenarcotic symptoms) and the symptoms which might be part of chronic organic solvent intoxication⁵. Furthermore, whereas cross-sectional study designs are commonly used in studies of these neurotoxic effects, it is often difficult to determine whether the reported symptoms reflect acute or chronic neurotoxic effects⁸.

Symptoms associated with acute effects, also called prenarcotic symptoms, are for example, sleepiness, nausea, vertigo, headache, incoordination and alcohol intolerance⁵.

Symptoms supposed to be associated with chronic neurotoxic effects may be classified in "core" and "additional" symptoms⁵. Core symptoms are fatigueability, bad memory, difficulties in concentration and loss of initiative. Additional symptoms often present are depression, dysphoria, emotional lability, headache, irritation, sleep disturbances, paraesthesia and vertigo⁵.

These symptoms might be the first signs of organic solvent intoxication. An international working group suggested that workers suffering from these symptoms, without any other objective evidence of neurological damage, should be diagnosed as suffering from organic solvent intoxication, type I^{5,6}. The objective of the present study is to compare a population of Dutch solvent exposed workers with a non-exposed population with regard to the prevalence of prenarcotic and neuroathenic symptoms in order to investigate the existence of acute and chronic neurotoxic effects due to exposure to organic solvents.

MATERIAL AND METHODS

A case-control study was conducted in The Netherlands to investigate whether Dutch painters are at increased risk of developing mental disorders due to organic solvent exposure. Both cases and controls were selected from Dutch painters and construction workers organizations. These organizations were founded by employers and employees to execute several social laws. Cases were defined as men receiving disability benefits because of mental disorders. The control population consisted of a random sample of 1000 non-disabled men from the total population

of the painters and construction workers organizations.

Cases and controls were approached by telephone. Participants received a questionnaire. Questions were asked about their occupational history and exposure to organic solvents. Furthermore attention was given to the occurrence of prenarcoctic and neurasthenic symptoms related to exposure to organic solvents. The list of symptoms used in this investigation was based on Scandinavian symptom lists developed for that purpose⁹.

In the present study a comparison was made between the reported symptoms of the exposed and non-exposed control population. Similar data from the cases were not included in this study. Logically, cases suffering from mental disorders, whether or not this mental disorder was caused by organic solvent exposure, would report a high number of neurasthenic symptoms. Therefore, a comparison of cases and controls with regard to symptom reporting would not show useful additional information.

To compare the prevalence of symptoms and symptom groups between exposed and non-exposed workers Odds Ratios (OR) and confidence limits were calculated according to Schlesselman¹⁰. The statistical significance of differences between mean scores of symptom groups was tested by using Student's t-test. Pearson's coefficients of correlation were calculated to describe the association between symptom scores, age, workstress and three indices for the level of organic solvent exposure.

RESULTS

Data from 822 respondents, collected by means of questionnaires, were included in the study. At first a subdivision was made into two groups, based on information from the questionnaires about their occupational exposure to organic solvents. Exposure to organic solvents is encountered in several occupations in the construction industry. The highest levels of exposure within the construction industry are present among painters, carpet layers and road markers. Therefore only those who had worked for at least one year as a painter, carpet layer or road marker ($n = 379$) were classified as exposed to organic solvents; all others were classified as non-exposed ($n = 443$).

A comparison was made between the occurrence of prenarcoctic symptoms among exposed and non-exposed persons. Participants were asked to describe the situation

as experienced during the last year. Answers had to be chosen out of four categories: never, sometimes (e.g. once a month), regular (e.g. once a week) or often (more than once a week). Persons included in Table 1 scored regular or often on that particular question.

Table 1: Frequency distribution of prenarcotic symptoms among exposed and non-exposed subjects.

	Exposed (n = 379)	Non-exposed (n = 443)	OR	Confidence Limits ($\alpha = 0.05$)
Nausea	20	7	3.47	(1.45 - 8.28)
Vomiting	3	4	0.88	(0.20 - 3.96)
Dizziness	18	14	1.53	(0.75 - 3.12)
Drunken feeling	12	7	2.04	(0.79 - 5.24)
Headache	36	34	1.26	(0.77 - 2.05)
Shortness of breath	31	19	1.99	(1.11 - 3.58)
Absent mindedness	15	11	1.62	(0.74 - 3.56)
Misunderstanding of in- structions and jobs	4	6	0.78	(0.22 - 2.78)
Ear tingling	18	28	0.74	(0.40 - 1.36)
Difficulties with talking	3	5	0.70	(0.17 - 2.95)
Loss of appetite	22	8	3.35	(1.48 - 7.60)
Drowsiness	53	47	1.37	(0.90 - 2.08)
Alcohol intolerance	20	20	1.18	(0.62 - 2.23)

As may be seen from this Table three symptoms were significantly more frequent among the exposed persons: "nausea", "shortness of breath" and "loss of appetite". Those who had scored often on one or more of the prenarcotic symptom questions were asked whether their complaints ceased during weekends and holidays. This question was positively answered by 50 (13.2 %) of the exposed and 33 (7.4 %) of the non-exposed subjects.

The questionnaire contained 33 questions about the occurrence of neurasthenic symptoms. Scoring procedures were identical with those described in association with prenarcotic symptoms. The results are shown in Table 2. Only three out of these 33 symptoms were significantly more frequent among the exposed subjects.

Table 2: Responses concerning neurasthenic symptoms associated with long-term organic solvent intoxication among exposed and non-exposed subjects.

	Exposed (n = 379)	Non-exposed (n = 443)	OR	Confidence Limits ($\alpha = 0.05$)
1. Do you get up tired in the morning?	70	60	1.45	(0.99 - 2.12)
2. Do you feel excess tiredness after the workday?	44	50	1.03	(0.67 - 1.59)
3. Are you forgetful?	36	29	1.50	(0.90 - 2.49)
4. Do you often forget what you intended to do?	27	22	1.47	(0.82 - 2.63)
5. Do you have to go back and check whether you turned off the gas, locked the door etc.?	47	55	1.00	(0.66 - 1.52)
6. Do you make notes of things you must remember?	61	76	0.93	(0.64 - 1.35)
7. Have your relatives or friends told you that you are forgetful?	16	17	1.10	(0.55 - 2.42)
8. Do your thoughts stray when you try to concentrate?	72	54	1.69	(1.15 - 2.48)
9. Do you fall asleep when watching television?	62	74	0.98	(0.68 - 1.42)
10. Are you lost in your own thoughts?	76	71	1.31	(0.92 - 1.87)
11. Do you notice that you are "daydreaming"?	31	30	1.23	(0.73 - 2.08)
12. Do you have difficulties understanding what you read in newspapers or books?	25	28	1.05	(0.60 - 1.84)
13. Do you have difficulties falling asleep?	32	27	1.42	(0.84 - 2.41)
14. Do you wake at night?	41	30	1.67	(1.02 - 2.74)
15. Do you have nightmares?	3	5	0.70	(0.17 - 2.95)
16. Does your mood change without reason?	28	16	2.13	(1.13 - 4.00)
17. Are you depressed?	17	14	1.44	(0.70 - 2.97)
18. Are you irritated?	33	30	1.31	(0.78 - 2.19)

Table 2 continued

	Exposed (n = 379)	Non-exposed (n = 443)	OR	Confidence Limits ($\alpha = 0.05$)
19. Are you restless?	46	50	1.09	(0.71 - 1.67)
20. Are you afraid?	14	8	2.09	(0.87 - 5.04)
21. Are you listless?	15	23	0.75	(0.38 - 1.46)
22. Are you drowsy?	47	43	1.32	(0.85 - 2.05)
23. Do you become tired among other people?	21	13	1.94	(0.96 - 3.94)
24. Do you have difficul- ties in starting a con- versation with others?	40	47	0.99	(0.63 - 1.54)
25. Do you suffer from headaches?	40	36	1.33	(0.83 - 2.13)
26. Do you suffer from dizziness?	15	18	0.97	(0.48 - 1.95)
27. Do you sweat without exerting yourself?	43	42	1.22	(0.78 - 1.92)
28. Do you have palpita- tions without exerting yourself?	12	9	1.58	(0.66 - 3.79)
29. Do your hands tremble?	21	26	0.94	(0.52 - 1.70)
30. Do you feel as though you have something in your throat?	15	16	1.10	(0.54 - 2.26)
31. Do you feel an oppres- sion on your chest?	24	20	1.43	(0.78 - 2.63)
32. Do you suffer from a diminished sexual inte- rest?	11	16	0.80	(0.37 - 1.74)
33. Do your legs feel numb or tingle?	23	34	0.78	(0.45 - 1.35)

The symptoms listed in Table 2 may be grouped into eight categories: fatigue, forgetfulness, concentration difficulties, sleeping difficulties, lability of mood, headache and dizziness, vegetative symptoms and neuropathy. For every person the scores (1, 2, 3 or 4) on every question within a symptom group were summarized. Subjects included in Table 3 scored above 50% of the maximum score (that is, number of symptoms times 4) of the relevant symptom group. Table 3 shows that using this approach a significant difference between exposed and non-exposed persons exists only with respect to "lability of mood" (OR = 1.69).

Table 3: Symptom groups: number of exposed and non-exposed subjects scoring more than 50% of the maximum summarized group score.

	Exposed (n = 379)	Non-exposed (n = 443)	OR	Confidence Limits ($\alpha = 0.05$)
Fatigue (1 - 2)*	85	76	1.40	(0.99 - 1.99)
Forgetfulness (3 - 7)	50	45	1.34	(0.88 - 2.05)
Concentration difficulties (8 - 12)	69	65	1.29	(0.89 - 1.87)
Sleeping difficulties (13 - 15)	29	24	1.45	(0.83 - 2.54)
Lability of mood (16 - 24)	44	32	1.69	(1.05 - 2.72)
Headache and dizziness (25 - 26)	31	31	1.18	(0.70 - 1.98)
Vegetative symptoms (27 - 32)	20	20	1.18	(0.62 - 2.23)
Neuropathy (33)	23	34	0.74	(0.45 - 1.35)

* Numbers refer to the symptoms as listed in Table 2 that are included in the relevant symptom groups.

Table 4: Comparison of mean scores of various symptom groups.

	Exposed	Non-exposed	P-value (Student's t-test)
Prenarcotic score	17.59	15.73	0.000
Symptom score	49.54	47.95	0.052
Fatigue	3.59	3.45	0.163
Forgetfulness	7.70	7.62	0.653
Concentration difficulties	8.43	8.11	0.070
Sleeping difficulties	4.20	4.11	0.325
Lability of mood	13.31	12.74	0.041
Headache and dizziness	3.02	2.85	0.026
Vegetative symptoms	7.93	7.74	0.233
Neuropathy	1.36	1.33	0.477

To make a more elaborate comparison between exposed and non-exposed subjects, mean scores of the symptom groups and of the total narcotic and prenarcotic symptom scores were compared. The significance of the difference was tested using Student's t-test. The results of this analysis, as shown in Table 4, indicate significant differences with respect to "prenarcotic score", "lability of mood" and "headache and dizziness" ($p < 0.05$). The differences between two other groups, total symptom score and concentration difficulties, are on the borderline of significance ($p < 0.10$).

Table 5: Correlation matrix (Pearson's coefficients of correlation) of prenarcotic score (PS), symptom score (SS), age (A), workstress (WS), duration of exposure (E), painters index (PI) and general exposure index (GEI).

I Exposed subjects (n = 379)

	PS	SS	A	WS	E	PI	GEI
PS	1.0000	0.7182**	-0.0771	0.3437**	-0.0891	0.1464**	0.2238**
SS		1.0000	0.0032	0.2961**	-0.0516	0.0727	0.1134
A			1.0000	0.0432	0.8496**	0.0507	0.0390
WS				1.0000	0.0486	0.1402*	0.1666*
E					1.0000	0.2128**	0.1302
PI						1.0000	0.4976**
GEI							1.0000

II Non-exposed subjects (n = 443)

	PS	SS	A	WS	GEI
PS	1.0000	0.6036**	-0.0170	0.2443**	0.1546*
SS		1.0000	0.0358	0.4226**	0.0988
A			1.0000	-0.0052	-0.0367
WS				1.0000	0.1589
GEI					1.0000

* = $p < 0.05$ (two-sided)

** = $p < 0.01$ (two-sided)

Finally, we examined whether the level of prenarctic and neurasthenic symptom reporting was associated with other factors, besides organic solvent exposure, such as age, workstress, duration of exposure, painters index and general exposure index. The painters index was based on information from the questionnaires about the involvement of painters in painting practices, such as paint spraying, using alkyd paints and paint removers, that may lead to high exposure to organic solvents. The general exposure index, calculated for all participants contained information about working activities and conditions associated with organic solvent exposure, but not exclusively related to the painting profession. Detailed information of these indices will be published elsewhere.

As shown in the correlation matrix (Table 5) a strong correlation exists among exposed and non-exposed subjects between the prenarctic and the neurasthenic symptom score. Furthermore, for both groups a correlation was observed between the symptom scores and workstress. No correlation was found between the neurasthenic symptom score and the level of organic solvent exposure as defined by the exposure indices. However, the prenarctic symptom score was correlated with the painters index and the general exposure index, but not with the duration of exposure to organic solvents.

DISCUSSION

The analysis of our study material shows some indications for a relation between organic solvent exposure and the occurrence of neurasthenic and prenarctic symptoms. A rough comparison between exposed and non-exposed participants with respect to the occurrence of all separate prenarctic and neurasthenic symptoms shows a weak association between these symptoms and exposure to organic solvents. Because long lists of symptoms were used some comparisons of symptom reporting between exposed and non-exposed persons will (purely as a result of chance) elicit statistical significant differences. However, nine out of thirteen prenarctic symptoms (69.2%) and 23 out of 33 neurasthenic symptoms (69.7%) indicate weak associations with organic solvent exposure, while the calculated Odds Ratio is greater than one. The fact that more exposed than non-exposed participants reported a decrease of prenarctic symptoms during weekends and holidays, points to the role of a work related factor, such as organic solvent exposure, in the origin of their symptoms.

After classifying the 33 neurasthenic symptoms in 8 symptom groups only "lability of mood" was reported statistically significantly more often by the exposed respondents. Here again the majority of the calculated Odds Ratios (87.5%) indicated weak associations between symptoms and organic solvent exposure. A more elaborate approach using mean scores instead of summarized scores to compare the symptom groups elicit greater differences between exposed and non-exposed participants. Particularly the differences between the mean total prenarcotic score ($p < 0.0001$) and mean total neurasthenic symptom score ($p \leq 0.05$) attract attention. Apparently the prenarcotic symptom score is associated with the various exposure indices, while this association can not be confirmed for the neurasthenic symptom score. Furthermore the neurasthenic and prenarcotic symptom score are both mutually related and related to the level of workstress.

While interpreting these results the shortcomings of this study should be kept in mind. Firstly, information bias may have influenced our results. Before our investigation attention was given in The Netherlands to the risks of neurological damage from long-term organic solvent exposure. Thus, solvent exposed workers might have had a tendency to report more complaints. Secondly, the detection of positive associations between symptoms and organic solvent exposure, as reflected by statistically significant raised Odds Ratios or correlation coefficients, does not prove the existence of a causal relationship. Finally the "exposure indices" and "workstress" as introduced in the correlation matrix may be criticized because, as always, they are imperfect measures of the real situation. However, compared with other studies the introduction of these factors in the analysis of symptom reporting is an improvement.

In conclusion our study confirms the existence of acute neurotoxic effects among solvent exposed workers, as reflected by the occurrence of prenarcotic symptoms. However the study gives only limited evidence for the existence of chronic neurotoxic effects as reflected by the occurrence of neurasthenic symptoms, due to long-term exposure to organic solvents. Compared with Scandinavian studies the detected associations are rather weak. Furthermore the nature of these symptoms is not consistent with the classification of the WHO⁵, the relations are stronger for additional symptoms (lability of mood, headache, vertigo) as for the real core symptoms (memory and concentration difficulties). Besides, the role of workstress in the development of these neurasthenic symptoms among both exposed and non-exposed workers should be further examined.

Therefore it seems justifiable to conclude that the organic solvent syndrome type I, characterized by the occurrence of these symptoms without any neurological damage⁶, is not a frequently occurring occupational disease among Dutch solvent exposed workers.

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CHAPTER 9

ORGANIC SOLVENT EXPOSURE AND PREMATURE DISABILITY DUE TO NEUROPSYCHIATRIC DISORDERS:

State of the art in epidemiological research.*

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ABSTRACT

A review is presented of all epidemiological studies investigating the relationship between organic solvent exposure and premature disability due to neuropsychiatric disorders. The overall relative risk for exposed workers compared with non-exposed workers was calculated to be 1.64 for all neuropsychiatric disorders and 2.40 for neurotic disorders. However, the results of the concerned studies might be influenced by a considerable amount of bias, hampering the interpretation of the presented data. Despite all critical notes that can be expressed with respect to the applied study designs and the validity of the results, the existence of an increased risk for disability benefits, especially among highly exposed workers, can not be excluded.

INTRODUCTION

Chronic neurotoxic effects due to long-term organic solvent exposure have received substantial scientific and public interest during the past fifteen years. Several articles thoroughly reviewing this issue have been published^{1,2}. However, there is still a lack of international agreement with respect to the existence and the nature of these effects³.

From the nature of the syndromes supposed to be associated with long-term exposure to organic solvents, such as presenile dementia and the psycho-organic syndrome, emerges the question whether the involved exposed workers are at higher risk for being prematurely disabled due to neuropsychiatric disorders.

So far the relationship between organic solvent exposure and premature disability due to neuropsychiatric disorders has been investigated in 4 Scandinavian and 1 Swiss study⁴⁻⁸. Recently a Dutch case-control study has been carried out investigating the same relationship⁹. All Scandinavian studies reveal positive relationships, whereas the studies conducted outside Scandinavia do not reveal such clear positive relationships between organic solvent exposure and neuropsychiatric disorders. The objective of this study is to compare and to discuss the various study designs and study results in order to find indications for the origin of these contradicting results and to determine the validity of the studies involved.

THE EPIDEMIOLOGICAL STUDIES

The epidemiological studies discussed in this review have either a case-control or a cohort design. Both study designs can be classified as forms of observational longitudinal epidemiological research. Prior to a short description of each study, some general information regarding the relevant study designs will be provided.

In the case-control approach the investigator must first define the disease of interest. Subsequently it must be established who are the cases of the particular disease and what group will serve as the control group. Next, information should be collected on past exposure of the cases and controls. In this approach the epidemiologist seeks to uncover differences in exposure between cases and controls. In the cohort approach the investigator first identifies a population that has experienced a particular exposure and then determines the subsequent health outcome. Morbidity or mortality rates in the cohort are then compared with those in some less exposed section of the cohort, with those in another non-exposed cohort or with the health experience in the general population¹⁰.

CASE-CONTROL STUDIES

The first case-control study on neuropsychiatric disorders among workers exposed to solvents was conducted in Sweden, using data from a regional pension fund⁴. A restriction was made to skilled workers in various trades with some connection to the construction industry. Cases were defined as individuals receiving a disability pension because of some type of mental disorder, whether or not in combination with somatic disorders. Mental disorders of obvious somatic origin, such as dementia from a traumatic brain injury, encephalitis etc. and primary disability, schizophrenia or manic-depressive psychosis were excluded from the study. However, cerebral atrophy, headache of unknown origin and unspecified vertigo were accepted as cases. If other neuropsychiatric disorders occurred in combination with alcoholism, alcoholism was considered as the main diagnosis. The cases were classified by the authors, according to the WHO-classification (ICD-8). Referents received a disability pension on the basis of some other disease, whereas the information in the register showed no indication of any kind of mental disorder.

The age criteria for cases and controls were set at 35 and 64 years. The timespan covered the years 1969 through 1973. Exposure was defined as years of painting, varnishing or carpet laying, as obtained from the pension register files. The study included 151 cases and 248 controls. The Odds Ratio was 1.8 for neuropsychiatric disorders and did not change when the cases of alcoholism were excluded from the analysis. A dose response relationship was indicated by the elevated Odds Ratio with increasing duration of exposure.

A similar study design was applied in a Finnish case-control study⁶. Cases and controls were selected from the register of the Finnish Employment Pension Fund. The age limits were set at 35 and 64 years. The cases comprised of all male construction workers who had been granted a disability pension because of certain neuropsychiatric disorders during the period 1978-1980. The disease categories included in this study were the same as in the investigation by Axelson et al⁴. Alcoholism was also treated similarly to the former study. The referents were selected from the construction workers who had been granted a disability pension for reasons other than neuropsychiatric disorders. Cases and controls were matched pairwise with regard to the starting date of pension and age at that date within the range of two years. The material consisted of 374 pairs. Information on occupation, as obtained from the registers, was used as indicator of solvent exposure. Painters and carpet layers were regarded as being exposed. The results of this study indicated that solvent exposure increases the risk of being prematurely disabled due to neuroses, but early pensioning due to alcoholism or other neuropsychiatric disorders is not increased by solvent exposure. Furthermore no dose response relationship was found.

Another case-control study on neuropsychiatric disorders among workers exposed to solvents was conducted in Denmark⁸. Data were obtained on all members of the carpenter and cabinet makers trade union who received disability or early old age pensions during the period January 1, 1971 to December 31, 1975. Diagnoses were obtained from official hospital records through linkage. Cases were selected as disability and early old age pensioners with the following primary or secondary diagnoses: psychoses, neuroses, changes of character, oligophrenia, mental retardation and diseases of the nervous system or sensory organs. Controls, matched on type of pension and age, were selected from union members with other diseases who were also pensioned during the same time period.

From a total of 412 eligible study subjects, 342 (i.e. 287 disability pensioners and 55 old age pensioners) could be located in 1978. Information regarding occu-

pational exposure and vocational training was obtained both directly from the study subjects by means of a questionnaire and from the files of the trade union. An employment history suggesting 4,000 hours of work with organic solvents was the criterion used to define highly exposed subjects. The results are presented for different groups of pensioners, different sets of case entities and different criteria of exposure. The Odds Ratio for neuropsychiatric disorders in former employees with high indoor exposure was 2.8. Cabinet makers, and especially cabinet makers with high exposure to lacquers and glues, had a higher risk of receiving a disability pension for a neuropsychiatric disease than carpenters. The calculated Odds Ratios were adjusted for differences in age, alcohol consumption and previous head injuries.

Recently a Dutch case-control study was undertaken to verify the results obtained in Scandinavian countries and to determine the current situation in The Netherlands⁹. The population base was defined as the Dutch Painters and Construction Workers Organizations that are responsible for the payment of disability benefits. Cases were defined as male persons receiving disability benefits due to some neuropsychiatric disorder as from a date between 1 July 1984 and 1 July 1986. All diagnoses, as described in group V of the WHO-Classification of Diseases (9th revision), were accepted as cases. The control population consisted of a random sample of 1,000 persons from the total population base, taking into account the differences in population size and age distribution between the painters and construction workers organizations.

Questionnaires were used to collect information about vocational training, occupational history, exposure to organic solvents and the presence of potential confounding factors. 252 Cases (response: 61.6%) and 822 controls (response: 69.7%) participated in the study by returning completed questionnaires. Painters, carpet layers and road markers were classified as the exposed group, while all other occupations were considered non-exposed.

The Odds Ratio for all neuropsychiatric disorders ($OR = 1.17$) did not reveal an increased risk for painter to receive disability benefits due to neuropsychiatric disorders. An increased OR was detected with respect to neuroses ($OR = 2.3$), whereas the risk to become disabled due to another frequently diagnosed neuropsychiatric disorder, adjustment reactions was decreased among painters ($OR = 0.86$). The Odds Ratios were adjusted for differences in age, education level, marital status, smoking habits, alcohol consumption and Quetelet-index. The analysis of dose-response relationships showed no elevated risk with increasing duration of exposure. However, using more detailed information about organic solvent exposure, some tendencies towards positive dose response relationships were revealed.

COHORT STUDIES

A cohort study of the risk of disability among painters with special regard to disabling presenile dementia as an occupational disease was conducted in Denmark⁷.

A cohort of 2,601 male painters and 1,790 male brick layers from the Copenhagen area was identified and followed during the period January 1, 1971 - December 31, 1975. In this period the incidence of disability pensioning was examined for the two occupational groups and for a referent population of all Copenhagen men over 30 years of age.

The painters were found to have an increased relative risk to three neuropsychiatric diagnostic groups, namely psychosis, diseases of the nervous system (excluding epilepsy) and neurosis, personality disorders etc. The increase was significant in all three diagnostic groups in comparison to both referent groups. The pension diagnoses were later reclassified by the authors in order to extract all cases of "presenile dementia" from the neuropsychiatric diagnoses. According to the author's reclassification half of the painters had a diagnosis of presenile dementia and the risk ratio was 2.8 compared to the brick layers.

Recently the results have been published of a Swiss cohort study among Geneva painters and electricians⁵. The 1,916 painters and 1,948 electricians who resided in the Canton of Geneva at the time of the 1970 census, were identified and followed up to 1984. During the study period 121 disability pensions were awarded to painters and 59 to electricians. Disability due to neuropsychiatric disorders gave a risk among painters of 1.8 relative to the risk among electricians. Solvent exposure, however, was confounded with alcoholism which was associated with neuropsychiatric disorders in 12 of 20 painters and only one of 10 electricians. The results of the six studies discussed above are summarized in Table 1.

RISK ASSESSMENT

The results of the epidemiological studies indicate an increased risk for organic solvent exposed workers to be prematurely disabled due to neuropsychiatric disorders.

Table 1: Results of epidemiological studies of the relationship between organic solvent exposure and premature disability due to neuropsychiatric disorders.

First author + country	Study design	Neurotic disorders etc.		All included neuro-psychiatric disorders		Dose-response relationships	
		Number of exposed cases	OR/RR	Number of exposed cases	OR/RR		
Axelsson (1976) Sweden	Case- Control (n = 158) Control (n = 248)	6	1.1	35	1.8*		+ (number of years)
Mikkelsen (1980) Denmark	Cohort 2,601 painters 1,790 brick layers	21	2.8*	67	2.3*		Not investigated
Olsen (1980) Denmark	Case- Control (n = 141) Control (n = 146)	?	3.1*	?	2.8*		+ (hours of indoor exposure to organic solvents)
Lindström (1984) Finland	Case- Control (n = 374) Control (n = 374)	12	5.5*	36	1.6		- (number of years)
Gubéron (1989) Swiss	Cohort 1,960 painters 1,948 electricians	11	1.7	20	1.8		Not investigated
van Vliet (1989a) The Netherlands	Case- Control (n = 252) Control (n = 822)	38	2.3*	117	1.2		- (number of years) + (exposure indices)

* $P < 0.05$

However, the estimate of the strength of this relationship varies considerably from one study to another.

It is possible to combine these separate risk estimates into one overall risk assessment. Therefore a weighing factor can be applied in accordance to the study size. In this instance, the number of exposed cases of respectively neurotic disorders and all included neuropsychiatric disorders was used as the weight for each study (Table 1). Unfortunately, the relevant data were not available from the study of Olsen and Sabroe⁸. The combined relative risk was obtained by dividing the sum of product of the weight and the relative risk (OR/RR) by the sum for the weights. By this procedure an overall relative risk for all neuropsychiatric diagnoses was calculated to be 1.64 and for neurotic disorders 2.70.*

GENERAL DISCUSSION

As stated earlier, the results of the epidemiological studies described in this paper seem to indicate an increased risk for premature disability due to neuropsychiatric disorders among workers exposed to organic solvents. However, the results of these studies could be influenced by a considerable amount of bias which hampers the interpretation and the validity of the presented data.

The control groups used in the Scandinavian case-control studies consisted of persons receiving disability benefits for reasons other than neuropsychiatric disorders. If some non-solvent occupations, e.g. brick laying, demands greater physical exercise, this could lead to more disability benefits due to for instance musculo-skeletal disorders among the non-exposed group. Consequently, a relative underrepresentation of solvent exposed workers will occur in the control group, leading to an artificial increase of the Odds Ratio^{4,11}. This, perhaps rather hypothetical pitfall, was avoided in the Dutch case-control study by selecting healthy persons receiving no disability benefits as controls.

* Neuropsychiatric disorders:

$$\text{Overall RR} = \frac{(35 \times 1,8) + (67 \times 2,3) + (36 \times 1,6) + (20 \times 1,8) + (117 \times 1,2)}{35 + 67 + 36 + 20 + 117} = 1,64$$

Neurotic disorders:

$$\text{Overall RR} = \frac{(6 \times 1,1) + (21 \times 2,8) + (12 \times 5,5) + (11 \times 1,7) + (38 \times 2,3)}{6 + 21 + 12 + 11 + 38} = 2,70$$

Furthermore the choice of the type of occupation may introduce bias. It can not be excluded that determinants for later disability pension, such as education, intelligence, personality, health, are associated with the earlier choice of occupations. Bias may result if persons predisposed to psychiatric diseases are more likely to choose occupations involving exposure to organic solvents^{7,8}.

Another possible source of bias could have occurred if solvent exposed workers suffering from neuropsychiatric symptoms are more likely to change jobs than solvent exposed workers without these symptoms. This so called "healthy worker effect" may conceal an existing association^{7,8}.

Otherwise, selection bias can result from a large non-response among the approached cases and controls, as occurred in the Dutch case-control study. However, the non-response of cases and controls was equally divided among the painters (mainly exposed) and construction workers (mainly non-exposed) organization, thus diminishing the probability that selection bias has influenced the study results. The classification of neuropsychiatric disorders by social security physicians is another source of potential bias. The physicians granting disability benefits are no trained psychiatrists and diagnostic difficulties may easily arise in the broad field of neuropsychiatric disorders. Furthermore, awareness of the association between organic solvent exposure and neuropsychiatric disorders among the physicians might facilitate diagnosing neuropsychiatric disorders among solvent exposed workers. This effect, leading to an overestimation of the risk, could have influenced the results of studies conducted after the publication of the Scandinavian reports, introducing the organic solvent syndrome as an "occupational disease". However, the concerning studies^{5,6,9} show, compared to the former studies, no increased risk for neuropsychiatric disorders among solvent exposed workers.

Except for the study of Van Vliet et al⁹, diagnostic codes related to the 8th revision of the International Classification of Diseases were used to classify the cases. However, the codes or groups of codes included in the studies varied, thus restricting the comparability of the results. Furthermore, reclassification by the authors, with awareness of exposure status, might have introduced further possibilities towards the occurrence of classification bias^{4,7}.

Union files and registers or information from participants were used to collect information about the presence or absence of solvent exposure. Existing knowledge of the neurotoxic effects of organic solvents may have biased the selfreported information of the cases. Again, this bias could have influenced in particular the recently conducted case-control study⁹.

The possible influence of confounding factors has not been thoroughly examined

in most studies. Only two studies^{8,9} have included other factors than age in the analysis. Evaluation of the role of alcohol consumption which is an important neurotoxic agent, leads to contradictory results. The Scandinavian authors more or less exclude alcohol abuse as an important confounding factor, whereas the Swiss study suggests that the association between solvent exposure and neuropsychiatric disorders was confounded by alcoholism. There is no clear explanation for this discrepancy. Perhaps the officially propagated negative attitude towards alcohol consumption in Scandinavian countries promotes underreporting of alcohol consumption. The possible synergism of solvents effect and alcohol emphasizes the importance of considering the effect of alcohol as a possible confounding factor. Beside alcohol consumption, other factors such as gender, ethnicity, constitutional factors, are recommended to be studied in relation to neuropsychiatric disorders and organic solvent exposure¹². The Dutch case-control study indicated the importance of workstress as a confounding factor.

The analysis concerning dose-response relationships revealed varying results. However, it must be emphasized that the number of years is a very crude estimate of the intensity of exposure. The use of more detailed and accurate data of solvent exposure may yield different results as became evident in the Dutch case-control study.

Certainly, a comparison between the results of studies conducted inside and outside Scandinavia shows some differences. The Swiss authors conclude that their data reveal inadequate evidence to support the existence of a solvent related neuropsychiatric syndrome among Geneva painters. The Dutch authors do not rule out the possibility of a neuropsychiatric effect among a small group of highly exposed painters. However, they are not convinced that the increased risk among painters with respect to disability due to neurotic disorders is related to organic solvent exposure. Misclassification bias has been postulated to be an alternative explanation for this relationship¹³.

There is no clear explanation for the discrepancy described above. Differences in study design (e.g. including of healthy controls and more potential confounding factors in the Dutch case-control study) might play a role. Furthermore, it must be kept in mind that disability is the result of a process involving both medical and social factors. The disability systems differ from one country to another, thus perhaps introducing varying amounts of selection bias. On the other hand, some authors¹⁴ state that in the past exposure to organic solvents has been very high in Scandinavian countries compared with other European countries due to differences in working conditions (more interior work and spray painting).

CONCLUSIONS

The results of the studies investigating the relationship between organic solvent exposure and premature disability due to neuropsychiatric disorders may be influenced by a considerable amount of bias. Selection-, information- and misclassification bias may have worked in various directions, leading to overestimations or underestimations of true associations.

An overall estimation indicates a stronger association with neurotic disorders than with all neuropsychiatric disorders included in the relevant studies. This trend is confirmed by a recent case-control study carried out in The Netherlands, which took into account some of the criticisms against the Scandinavian studies. However, the relationship between organic solvent exposure and neurotic disorders evokes some questions. It might be taken as an indication for some preexposure susceptibility towards neuropsychiatric disorders among persons choosing occupations involving organic solvent exposure, because neurotic disorders are related to character and personality characteristics.

On the other hand, it is possible that neurotoxic effects of organic solvent exposure diminish the ability of the involved workers to cope with stress. This could lead to disproportionate (neurotic) reactions to daily life stress among the affected solvent exposed workers.

All in all, the existence of chronic neurotic effect of organic solvent exposure leading to premature disability can not be excluded, especially not among highly exposed subjects. In view of the seriousness of the effects, efforts should be made to control organic solvent exposure among solvent exposed workers.

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CHAPTER 10

SUMMARY AND CONCLUDING REMARKS

SUMMARY AND CONCLUDING REMARKS

A case-control study has been carried out in order to investigate the relationship between premature disability due to neuropsychiatric disorders and organic solvent exposure, as experienced by Dutch painters.

The population base consisted of persons affiliated to the Dutch Painters Organization (SFS) and twenty percent of the persons affiliated to the Dutch Construction Workers Organization (SFB). Cases were defined as persons receiving disability benefits due to a diagnosis from the diagnostic main group of neuropsychiatric disorders. The control population consisted of a stratified sample from the population base (non-cases) taking into account differences in population size and age distribution between the painters- and construction workers organization. 252 Cases and 822 controls participated in the study.

By means of questionnaires information was collected from the participants about their occupational history, exposure to organic solvents, pre-narcotic and neuroathenic symptoms and the presence of potential confounding factors, such as education level and alcohol abuse. The risk to receive disability benefits due to neuropsychiatric disorders was not increased for exposed workers, compared to non-exposed workers (OR = 1.01). Adjustment for a number of confounding factors increased the Odds Ratio (OR = 1.17), but not to a level indicating a statistically significant association between occupational exposure to organic solvents and neuropsychiatric disorders leading to long-term disability.

A subdivision of the main group of neuropsychiatric disorders in different diagnostic categories revealed a statistically significant increased risk among exposed workers to receive disability benefits due to neurotic disorders (OR = 2.30). However, other diagnoses that may not be readily distinguishable from neurotic disorders (e.g. ICD-309: adjustment reactions) were more often awarded to non-exposed persons. A combination of these diagnoses did not show an increased risk for painters. Therefore it can not be excluded that the detected association between organic solvent exposure and disability due to neurotic disorders may have been the result of classification bias.

In the Scandinavian countries three case-control studies with a somewhat similar study objective and study design have been carried out. Axelson et al¹ and Olsen and Sabroe² observed an increased risk among solvent exposed workers to be prematurely disabled due to all (non-specific) neuropsychiatric disorders. The study of Lindström et al³ revealed an association with neurotic disorders, but not with other neuropsychiatric disorders. The results of the study reported here are in

close agreement with the study carried out by Lindström et al³. However the association detected in this Finnish study (OR = 5.5) is stronger than the association emerging from our study (OR = 2.3).

Beside resemblances in study design with these Scandinavian studies some differences can be mentioned:

- The use of different ICD-codes for the cases (ICD-8 versus ICD-9);
- Differences between The Netherlands and Scandinavia in organization and execution of the disability pension system;
- The choice of a different control group ("healthy" versus "disabled" persons).

Therefore caution must be taken while comparing our study results with the Scandinavian studies.

The detection of a statistically significant association between organic solvent exposure and neuropsychiatric disorders is no guarantee for the existence of a causal relationship. The final proof for a causal association can only be given by experimental research. In view of the lack of experimental data a judgement must be made by weighing the available evidence⁴. This weighing should include additional information beside the strength of the association as revealed by the study. Always, great value is given to the existence of a dose-response relationship. In case of a causal relationship one might assume that the risk to develop an 'organic solvent syndrome' increases with higher and longer exposure to organic solvents. From the literature a number of indications point to the existence of such dose-response relationships^{1,2}. Ørbaek et al⁵ stated that the organic brain syndrome due to organic solvent exposure could develop after at least 10 years of occupational solvent exposure. Our study did not show a relationship between exposure dose, expressed in duration of exposure (years) and the risk of premature disability due to neuropsychiatric disorders. Lindström et al³ who also, as mentioned before, detected an increased risk for neurotic disorders, likewise did not observe a positive dose-response relationship. However the translation of exposure dose into the number of working years is a crude estimate of exposure. Not every painter will be exposed to the same level of organic solvents. In the analysis of our data an effort has been made to quantify this individual variation by the introduction of the painters index. This painters index is based on information from the questionnaires about painters activities assumed to be associated with high exposure to organic solvents.

Not only painters, but also other construction workers may regularly work with organic solvents or organic solvent containing products (such as glues). Therefore a "general" exposure index, taking into account these exposures, was con-

structed. With regard to the painters index a positive dose-response relationship was detected. A higher value of this exposure index appeared to be associated with a higher risk of receiving disability benefits due to neuropsychiatric disorders. However, high values of this painters index were only found among a small group of painters.

Strikingly, a positive dose-response relationship of the general exposure index could be demonstrated for painters, but not for other construction workers. Possibly the exposure of painters to organic solvents is, even at the same level of this general exposure index, more intensive than among construction workers. A construction worker indicating that he worked four or more times a week with organic solvents may for instance mean four brief moments, while a painter giving the same answer to this questions might have worked four whole days with organic solvents. Further analysis into the contributing elements of the painters index elucidated that the increased risk to be prematurely disabled due to neuropsychiatric disorders⁶ was mainly connected to "working with the paintspray" and "working with paint removers". Some other painting activities were also associated with elevated odds ratios, particularly working in poorly ventilated rooms. Poor ventilation can certainly contribute to the development of high concentrations of organic solvents in the workplace. However, in view of the limitations of this analysis no far-reaching conclusions may be drawn from this data.

The analysis revealed some indications that the possible increased risk of painters to be prematurely disabled due to neuropsychiatric disorders is not, or not exclusively, caused by exposure to organic solvents. Perhaps the workstress among painters is an important factor. Design and contents of the questionnaire used in this study were not primarily directed to establish the level of workstress to which the participants were exposed. The questions included in the questionnaire with regard to workstress can only give a superficial impression of the present workstress. Furthermore, decompensation by stressfactors needs not to contradict a possible neurotoxic effect of long-term exposure to organic solvents. Symptoms arising from this neurotoxic effect (such as forgetfulness, concentration disturbances, loss of initiative) may introduce problems in work- and private live, while on the other hand the neurotoxic effect of organic solvents may lead to a decreased stresstolerance, thus leading to earlier decompensation. Another finding emerging from this study concerns the statistical significant increased OR of "working more than one day a week with other paints" and "more than one day a week burning off paints". As stated earlier no far reaching conclusions may be drawn from this part of the analysis. However, these results raise the question whether within the painting trade other potentially neurotoxic

exposures (such as lead exposure) play a role in the development of neuropsychiatric disorders.

The analysis of prenarcotic and neurasthenic symptoms indicated that these symptoms occur more often among the exposed control population than among the non-exposed control population. The occurrence of such symptoms among workers occupationally exposed to organic solvents is in accordance with internationally published study results⁵⁻⁸. Within the exposed control population a correlation was found between the prenarcotic (acute) symptom score and the various exposure indices. However, such a correlation was not detected between the neurasthenic (chronic) symptom score and the painters- and general exposure index. None of the symptom scores were correlated to the duration of exposure. The strong correlation among the exposed and non-exposed control population between workstress and the acute/prenarcotic symptom scores was a remarkable finding.

In the above, it has been suggested that the relationship between organic solvent exposure and neurotic disorders, as emerging from our study results, may have been caused by classification bias. An additional analysis using information from the questionnaires revealed no indication to support the existence of a causal relationship between neurotic disorders and organic solvent exposure. The exposure of cases diagnosed as suffering from neurotic disorders did not appear to be higher or more intense than the exposure of cases diagnosed as suffering from other neuropsychiatric disorders. Furthermore, the symptoms reported by cases with neurotic disorders were not more in accordance with the symptoms attributed to the 'organic solvent syndrome'⁹ than the symptoms reported by cases with other neuropsychiatric disorders. The development of neurotic disorders might be related to some predisposing character structure¹⁰. Perhaps people with susceptibility to develop neuropsychiatric disorders tend to choose a job as a painter. However, on the basis of this study no pronouncement can be done with regard to the existence of differences in character structure between painters and construction workers.

Self-evidently attention must be given to the limitations of the study design. The case-control study design is rather sensitive to bias. This bias might have lead to an overestimation, but certainly also to an underestimation of the detected association between organic solvent exposure and neuropsychiatric disorders. Another limitation concerns the choice of the cases group. Attention was focussed on persons with neuropsychiatric disorders who receive disability benefits, indicating the existence of a prolonged and serious neuropsychiatric disease. It is possible that minor manifestations of the organic solvent syndrome not leading to prolonged disability were not detected in this study.

To conclude, it must be stated that the existence of a small increased risk among painters to be prematurely disabled due to neuropsychiatric disorders can not be excluded. The increased risk applies especially to painters who are exposed to high concentrations of organic solvents due to their working conditions or working practices. However, the detected associations are weaker than those emerging from the Scandinavian studies. Furthermore, the increased risk is restricted to the small group of painters with the highest organic solvent exposure. Among exposed workers the existence of prenarctic (acute) symptoms due to organic solvent exposure is more clearly demonstrable than the occurrence of neurasthenic (chronic) symptoms. Furthermore it must be taken into account that other factors (e.g. workstress) might play a role in the increase of the risk among painters to be prematurely disabled due to neuropsychiatric disorders.

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CHAPTER 11

PSYCHISCHE AANDOENINGEN ONDER SCHILDERS; RESULTATEN VAN EEN PATIENT-KONTROLE ONDERZOEK* (NEDERLANDSE SAMENVATTING)

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SAMENVATTING

Om na te gaan of er een verband bestaat tussen vroegtijdige arbeidsongeschiktheid (WAO-intrede) op grond van psychische aandoeningen en het werken met organische middelen is een patiënt-kontrole onderzoek verricht onder personen die zijn aangesloten bij het Sociaal Fonds Schildersbedrijf en het Sociaal Fonds Bouwnijverheid.

Het risico voor schilders op WAO-intrede tengevolge van psychische aandoeningen is, vergeleken met andere bouwvakkers, niet statistisch significant verhoogd (OR = 1,17). Als er al sprake is van een verhoogd risico bij schilders op neurotoxische effecten die tot WAO-intrede leiden, dan is het verhoogde risico beperkt tot de (kleine) groep schilders met de hoogste blootstelling aan organische oplosmiddelen.

Onder blootgesteld~~e~~ werknemers uit de controlepopulatie is het bestaan van akute (prenarkotische) klachten tengevolge van blootstelling aan organische oplosmiddelen duidelijker aantoonbaar dan het optreden van chronische (neurasthene) klachten. Bovendien moet rekening worden gehouden met het feit dat andere factoren (bijv. werkstress) een rol kunnen spelen in het ontstaan van deze klachten en in een eventuele verhoging van het risico voor schilders op WAO-intrede door psychische aandoeningen.

INLEIDING

Schilders vormen binnen Nederland een beroepsgroep van circa 35.000 werknemers¹. Gezien de aard van hun werkzaamheden worden zij vrijwel dagelijks blootgesteld aan organische oplosmiddelen. In een voorgaand artikel is uitgebreid ingegaan op de akute en chronische neurotoxische effecten van langdurige blootstelling aan organische oplosmiddelen².

Het meeste onderzoek naar chronische neurotoxische effecten van langdurige blootstelling aan organische oplosmiddelen is uitgevoerd in Scandinavië, alwaar het 'organic solvent syndrome' t.g.v. blootstelling aan organische oplosmiddelen in de zeventiger jaren als een officiële beroepsziekte is erkend en criteria zijn uitgewerkt voor het stellen van deze diagnose³. Op een bijeenkomst van een WHO-werkgroep in Copenhagen, waarin de oplosmiddelenproblematiek centraal stond, werd

de uitvoering van epidemiologisch onderzoek, met name in landen waar het 'organic solvent syndrome' nog niet is erkend, genoemd als één van de "needs for further research"⁴. Bovendien was nader onderzoek in Nederland met betrekking tot de relatie tussen blootstelling aan organisch oplosmiddelen en het ontstaan van neuropsychiatrische aandoeningen gewenst toen Scheffers e.a.⁵ hun, in opdracht van de Stichting Arbouw, uitgevoerde verzuimonderzoek publiceerden. Uit dit onderzoek kwam naar voren dat schilders een 35% hogere kans liepen dan bouwvakkers om de maximale uitkeringstermijn van de ziektewet te halen op grond van psychische aandoeningen.

Bij het onderzoek van Scheffers e.a.⁵ zijn een aantal kanttekeningen te maken die samenhangen met de aard en kwaliteit van het gebruikte materiaal (d.w.z. routinematig verzamelde verzuimstatistieken). Bij de interpretatie van de onderzoeksresultaten moet dan ook de nodige voorzichtigheid in acht worden genomen. De Stichting Arbouw heeft daarom opdracht verleend aan de Vakgroep Arbeidsgeneeskunde van de Rijksuniversiteit Limburg om een diepgaander onderzoek uit te voeren naar de relatie tussen blootstelling aan organische oplosmiddelen en het ontstaan van psychische aandoeningen bij schilders.

De centrale vraag waarop dit onderzoek antwoord tracht te geven is of de Nederlandse schilders tengevolge van deze blootstelling aan organische oplosmiddelen een verhoogd risico lopen op WAO-intrede tengevolge van psychische aandoeningen. Tevens tracht dit onderzoek antwoord te geven op de vraag of onder aan organische oplosmiddelen geëxponeerde werknemers meer neurasthene en prenarkotische klachten voorkomen.

ONDERZOEKSOPZET

Dit onderzoek heeft de vorm van een patiënt-kontrole onderzoek. De eerste stap in de opzet van een patiënt-kontrole onderzoek is het afbakenen van de doelpopulatie, hier wordt bedoeld de populatie waaruit patiënten en controlepersonen afkomstig zullen zijn. Het patiënt-kontrole onderzoek is uitgevoerd onder werknemers die zijn aangesloten bij het Sociaal Fonds Schildersbedrijf (SFS) en het Sociaal Fonds Bouwnijverheid (SFB). Het is van belang dat er binnen de onderzoekspopulatie variabiliteit bestaat voor wat betreft blootstelling aan de mogelijke etiologische faktor, i.c. organische oplosmiddelen. De power (d.w.z. de statistische kans om een in werkelijkheid aanwezig verband in het onderzoek te

vinden) van een patiënt-kontrole onderzoek is o.a. afhankelijk van het aantal in het onderzoek betrokken cases en controlepersonen en van het percentage controlepersonen dat is blootgesteld (geweest) aan de mogelijke etiologische faktor (i.c. organische oplosmiddelen). De efficiëntie van een patiënt-kontrole onderzoek, gedefinieerd als een situatie waarbij zo min mogelijk cases en controlepersonen nodig zijn om in combinatie met een hoge power een aanwezig verband te vinden, is optimaal als ongeveer de helft van de controlepopulatie is blootgesteld aan de mogelijke etiologische faktor en de andere helft niet.

Er van uitgaande dat bij het SFS aangeslotenen in principe geëxponeerd zijn en de bij het SFB aangeslotenen in principe niet en dat het SFB ongeveer 7 x groter is dan het SFS, hoeft slechts 1/7 van de SFB-populatie in het onderzoek betrokken te worden.

Deze situatie is benaderd door van het SFB alleen werknemers in het onderzoek te betrekken wiens zesde cijfer van het registratienummer een 6 of 7 is (d.w.z. geboren op dag 06, 07, 16, 17, 26, 27 van enige maand). Op deze manier is slechts éénviufde van de SFB-populatie in de onderzoekspopulatie betrokken.

SELEKTIE VAN CASES EN KONTROLES

Patiënten (cases) zijn gedefinieerd als personen (mannen) uit de doelpopulatie die met ingang van een datum gelegen tussen 01-07-1984 en 01-07-1986 een arbeidsongeschiktheidsuitkering ontvingen op grond van een psychische aandoening. Bij ziekte van een werknemer meldt een bedrijf het ziektegeval bij zijn Sociaal Fonds. Het ziekteverzuim van schilders en bouwvakkers wordt begeleid door verzekeringsgeneeskundigen van de Sociale Fondsen. Bij voortdurende ziekte heeft men in de regel na 52 weken recht op een arbeidsongeschiktheidsuitkering.

De mate van arbeidsongeschiktheid wordt voor schilders en bouwvakkers vastgesteld door de Gemeenschappelijke Medische Dienst (GMD). De verzekeringsgeneeskundigen van de GMD kennen een diagnose toe die vervolgens, door speciaal hiervoor opgeleid administratief personeel, wordt omgezet in een diagnosekode. Voor deze codering wordt gebruik gemaakt van de "International Classification Diseases" (ICD, 9de revisie, 1975). De ziekten worden ingedeeld in 17 hoofdgroepen, waarvan hoofdgroep V de psychische aandoeningen omvat.

De controlepopulatie is opgebouwd uit een representatieve steekproef van 1.000 personen (mannen) uit de doelpopulatie, rekening houdend met de verschillen in

grootte en leeftijdsopbouw tussen SFS en SFB. Personen uit de controlepopulatie ontvingen géén WAO/AAW-uitkering.

DATAVERZAMELING

De verzameling van gegevens vond in dit onderzoek plaats met behulp van een vragenlijst. De vragenlijst die bij de uitvoering van het patiënt-kontrole onderzoek is gebruikt bestaat uit 44 vragen (Appendix 4).

In deze vragenlijst komen de volgende onderwerpen aan de orde:

- Personalialia;
- WAO/AAW-vragen;
- Opleiding;
- Beroep;
- Werkomstandigheden en expositie aan organische oplosmiddelen bij schilders;
- Expositie aan organische oplosmiddelen in overige beroepen;
- Klachten gerelateerd aan het werk (prenarkotische klachten);
- Gezondheidstoestand;
- Symptomen passend bij het 'organic solvent syndrome';
- Potentiële verstorende variabelen: Quetelet-index, alcoholgebruik, roken.

De cases en controlepersonen zijn schriftelijk én telefonisch benaderd met de vraag of zij aan dit onderzoek hun medewerking wilden verlenen. De keuze voor een gekombineerde schriftelijke én telefonische benadering werd ingegeven door de wens een zo hoog mogelijke respons (d.w.z. percentage van de benaderde personen die deelnemen aan het onderzoek) te bereiken.

RESPONS

In de periode tussen 01-7-1984 en 01-07-1986 zijn 505 mannen uit de totale onderzoekspopulatie arbeidsongeschikt geworden door psychische aandoeningen. Naast de steekproef van 1.000 controlepersonen kwamen dus 505 cases in aanmerking om aan dit onderzoek deel te nemen. Bij de benadering van de respondenten is uitgegaan

van personen die telefonisch bereikbaar waren. Het besluit om het onderzoek tot de telefonisch bereikbare groep te beperken is genomen toen bleek dat de respons binnen de niet telefonisch bereikbare groep op een bijzonder laag nivo bleef steken (ca. 20 à 30%).

Van de cases waren 409 personen (81%) en van de controles waren 822 personen (82,2%) telefonisch bereikbaar. De respons van de personen die werden benaderd voor deelname aan het onderzoek lag voor de cases op 61,6% en voor de controles op 69,7%. Voor de controlepersonen die wel telefonisch bereikbaar waren, maar niet aan het onderzoek wilden meedoen, zijn nieuwe controlepersonen getrokken, zodat de controlepopulatie uiteindelijk 822 personen omvat. Aangezien voor cases deze mogelijkheid niet bestond, bedraagt het aantal in het onderzoek betrokken cases 252.

RESULTATEN

1. Odds Ratios

De eerste stap in de analyse van de gegevens van het patiënt-kontrole onderzoek was na te gaan hoeveel van de in het onderzoek betrokken cases en controlepersonen blootgesteld zijn geweest aan de eventuele causale faktor. Toegespast op dit onderzoek: hoeveel cases en controlepersonen zijn beroepsmatig blootgesteld geweest aan organische oplosmiddelen?

Niet alle werknemers die zijn aangesloten bij het SFS zullen blootgesteld zijn geweest aan organische oplosmiddelen. Bovendien komt blootstelling aan organische oplosmiddelen ook voor in verschillende beroepen binnen de bouwnijverheid. De hoogste blootstelling treft men echter aan in de volgende beroepsgroepen:

- schilders
- wegmarkeerders
- tapijtleggers
- autosputters

In het kader van dit onderzoek zijn werknemers die ooit werkzaam zijn geweest in één van de bovenstaande beroepen gedefinieerd als "blootgesteld aan organische oplosmiddelen". Werknemers uit alle andere beroepsgroepen zijn hier gerangschikt onder de niet-geëxponeerden.

Hoofdgroep V, psychische aandoeningen, omvat een zestiental ICD-kodes. Het is niet duidelijk onder welke ICD-kode personen met een 'organic solvent syndrome' t.g.v. langdurige expositie aan organische oplosmiddelen gediagnostiseerd zullen worden. Daarom is voor alle ICD-kodes afzonderlijk, en voor verschillende groepen ICD-kodes, nagegaan of er een relatie met de expositie aantoonbaar is. Tabel 1 geeft een overzicht van de resultaten. Uit deze tabel blijkt dat alleen de ICD-kode "300" (neurosen) statistisch significant vaker aan de geëxponeerden (patiënten) is toegekend. Er zijn echter ook ICD-kodes, zoals "309" (situatieve of exogene reactie), die vaker aan de niet-geëxponeerden zijn toegekend.

De relatie tussen blootstelling aan organische oplosmiddelen en het optreden van psychische aandoeningen kan worden vertekend door de inwerking van verstoringende variabelen (confounders). Verstoringende variabelen kunnen een in de werkelijkheid niet bestaande associatie suggereren, dan wel een reëel bestaande associatie maskeren. Het is daarom belangrijk om verstoringende variabelen te identificeren en in de analyse te betrekken. Met behulp van de vragenlijsten is informatie verzameld omtrent een aantal factoren die als "potentiële confounders" kunnen worden gezien ten aanzien van de relatie tussen blootstelling aan organische oplosmiddelen en het ontstaan van psychische aandoeningen. Het betreft hier: leeftijd, burgerlijke staat, opleiding, Quetelet-index, alcoholgebruik en roken. Een statistische methode om deze factoren in de analyse te betrekken is de logistische regressie-analyse. Door middel van deze analyse wordt de Odds Ratio (OR) gecorrigeerd voor de invloed van deze variabelen.

In Tabel 2 is de gecorrigeerde Odds Ratio weergegeven voor een aantal (groepen) ICD-kodes. Uit deze tabel komen dezelfde trends naar voren: alleen het risico voor schilders om arbeidsongeschikt te worden t.g.v. neurosen (ICD-300) is statistisch significant verhoogd.

2. Dosis-respons relatie

De mate waarin werknemers zijn blootgesteld aan organische oplosmiddelen kan onderling sterk variëren. Bij de aanwezigheid van een causaal verband tussen blootstelling aan organische oplosmiddelen en het optreden van psychische aandoeningen mag worden verwacht, dat het risico hoger is voor werknemers die een hogere blootstelling aan organische oplosmiddelen hebben ondervonden. Er zijn géén exakte kwalitatieve en kwantitatieve gegevens voorhanden omtrent de blootstelling van de in dit onderzoek betrokken personen.

Tabel 1: Odds Ratios voor verschillende (groepen) ICD-kodes van de in het onderzoek betrokken populatie.

ICD-kode	Geëxponeerden		Niet-geëxpo- neerden		OR	Betrouwbaar- heidsinterval ($\alpha = 0,05$)
	n	(%)	n	(%)		
296: Manisch-depressieve psychose/involutie depressie	5	(4,3)	2	(1,5)	2,92	0,56-15,13
298: Overige en niet- gespecificeerde psychosen	1	(0,8)	0	(0,0)	-	-
300: Neurosen	38	(32,5)	23	(17,0)	1,93	1,13- 3,30
301: Persoonlijkheids- stoornissen	4	(3,4)	2	(1,5)	2,34	0,43-12,85
303: Alcoholverslaving	4	(3,4)	5	(3,7)	0,94	0,25- 3,53
304: Drugverslaving	2	(1,7)	0	(0,0)	-	-
306: Fysiologische functiestoornissen door psychische oorzaken	5	(4,3)	12	(8,9)	0,49	0,17- 1,40
307: Speciale symptomen en syndromen, niet elders vermeld	1	(0,8)	0	(0,0)	-	-
309: Situatieve of exo- gene reactie	54	(46,2)	85	(63,0)	0,74	0,51- 1,07
310: Psychische reactie t.g.v. organisch hersensletsel	0	-	1	(0,7)	-	-
311: Depressie niet elders vermeld	3	(2,6)	5	(3,7)	0,70	0,17- 2,95
296 + 298 ¹	6	(5,1)	2	(1,5)	3,51	0,70-17,49
303 t/m 311 ²	69	(58,9)	108	(80,0)	0,75	0,54- 1,05
300 + 309 + 311 ³	95	(81,2)	113	(83,7)	0,98	0,72- 1,33
Totaal: 290 t/m 311	117	(100,0)	135	(100,0)	1,01	0,76- 1,34
Totaal aantal controle- personen	379		443			

ad 1: 'psychosen'

ad 2: 'overige niet psychotische stoornissen'

ad 3: ICD-kodes passend bij de symptomatologie van het 'organic solvent syndrome'

Tabel 2: Ongecorrigeerde en gecorrigeerde (voor leeftijd, burgerlijke staat, opleiding, roken, alcoholgebruik en Quetelet-index) Odds Ratios voor verschillende groepen ICD-kodes.

	OR ¹	Betrouwbaarheids- interval ($\alpha = 0,05$)	OR ²	Betrouwbaarheids- interval ($\alpha = 0,05$)
Alle cases	1,01	(0,76 - 1,34)	1,17	(0,85 - 1,61)
ICD-300	1,93	(1,13 - 3,30)	2,30	(1,19 - 4,08)
ICD-309	0,74	(0,51 - 1,07)	0,86	(0,57 - 1,29)
ICD-300 + 309 + 311	0,98	(0,72 - 1,33)	1,16	(0,82 - 1,63)
ICD-300 t/m 311	0,75	(0,54 - 1,05)	0,85	(0,59 - 1,24)

¹ Ongecorrigeerde Odds Ratio

² Gecorrigeerde Odds Ratio

Wel is het mogelijk om met behulp van een aantal vragen uit het enquêteformulier een schatting te maken van de blootstelling aan organische oplosmiddelen. Voor deze analyse is de blootstelling "vertaald" in een drietal indices:

1. Het aantal jaren werkzaam in één van de beroepen die gepaard gaan met hoge blootstelling aan organische oplosmiddelen (schilder, tapijtlegger, wegmarkeerder, autospuiter);
2. Schildersindex. Deze index bestaat uit de sommatie van een aantal scores op vragen over werkzaamheden van schilders welke gepaard gaan met een hoge blootstelling aan organische oplosmiddelen. Het betreft het werken met alkydverven, afbijtmiddelen en de verfspuit. Een hoge score is een aanduiding voor een hogere blootstelling aan organische oplosmiddelen. De maximale score bedraagt 24.
3. Algemene expositie-index. Veel bouwvakkers komen, alhoewel zij niet in één van de "blootgestelde beroepen" werkzaam zijn, toch regelmatig in contact met organische oplosmiddelen. Zij werken bijv. in één ruimte met schilders of maken gebruik van lijmen, afbijtmiddelen, oplosmiddelen en ontvetters. De scores van de vragen die op deze factoren betrekking hebben, zijn bij elkaar opgeteld. De maximale score is 48. Deze vragen zijn door alle respondenten, inclusief de schilders, beantwoord. Een hogere score is een aanduiding voor een hogere blootstelling aan organische oplosmiddelen.

Voor elk van deze expositie-indices is gekeken naar het bestaan van een dosis-respons relatie. Daarbij is gecorrigeerd voor een aantal verstorende variabelen, te weten leeftijd, burgerlijke staat, opleiding, alcoholgebruik, roken en Quetelet-index. De analyse is uitgevoerd met behulp van logistische regressie. Er lijkt vrijwel géén verband te zijn tussen het aantal jaren dat men werkt onder blootstelling aan organische oplosmiddelen en het risico arbeidsongeschikt te worden tengevolge van een psychische aandoening. Wel is een duidelijke relatie aantoonbaar tussen de hoogte van de "schildersindex" en het risico om arbeidsongeschikt te worden t.g.v. psychische aandoeningen. Deze trend is statistisch significant ($P \leq 0,05$). Ook voor de algemene expositie-index is deze trend, zij het minder sterk, aanwezig ($P \leq 0,08$). Hoge waarden van deze expositie indices komen echter alleen voor in een kleine groep schilders en bouwvakkers.

Deze resultaten wijzen erop dat mogelijk de aard en/of intensiteit van de blootstelling aan organische oplosmiddelen een rol spelen in het ontstaan van chronische neurotoxische effecten. Het is daarom van belang te onderzoeken of bepaalde werkzaamheden van schilders een verhoogd risico veroorzaken ten aanzien van het arbeidsongeschikt worden tengevolge van psychische aandoeningen. Uit de betreffende analyse komen als belangrijkste risikofactoren naar voren: werken met afbijtmiddelen, met de verfspuit en werken in slecht geventileerde ruimten.

3. Gezondheidsklachten

Het enquêteformulier bevat een aantal vragen die betrekking hebben op neurasthene gezondheidsklachten, welke in de literatuur in verband zijn gebracht met het 'organic solvent syndrome'⁴.

Bij de analyse van deze symptomen is in eerste instantie gekeken naar de scores op deze vragen binnen de controlepopulatie. De onderliggende vraagstelling bij deze analyse is of onder blootgestelde werknemers (die niet arbeidsongeschikt zijn verklaard op grond van een psychische aandoening) meer neurasthene klachten voorkomen dan bij de niet-blootgestelde werknemers uit de controlepopulatie. Bij het voorkomen van meer neurasthene klachten is het risico wellicht groter om ooit afgekeurd te worden op grond van een "psychische aandoening". Het is echter niet goed mogelijk om door middel van deze symptomenlijst onderscheid te maken tussen akute en chronische neurotoxische effecten.

In Tabel 3 zijn de vragen weergegeven waarop de blootgestelde werknemers significant meer klachten aangeven dan de niet-blootgestelde werknemers.

Tabel 3: Neurasthene en prenarkotische klachten die significant vaker worden gerapporteerd door aan organische oplosmiddelen blootgestelde controlepersonen dan door de niet-blootgestelde controlepersonen.

	Blootgestelde kontroles (n = 379)	Niet-bloot- gestelde kontroles (n = 443)	OR	Betrouwbaar- heidsinterval ($\alpha = 0,05$)
Neurasthene klachten:				
- Snel afgeleid als men probeert zich te concentreren	72	54	1,69	1,15-2,48
- 's Nachts vaak wakker worden	41	30	1,67	1,02-2,74
- Stemmingsvermindering zonder directe aanleiding	28	16	2,13	1,13-4,00
Prenarkotische klachten:				
- Misselijk gevoel	20	7	3,47	1,45-8,28
- Kortademigheid	31	19	1,99	1,11-3,58
- Gebrek aan eetlust	22	8	3,35	1,48-7,60

Door middel van de vragenlijst is tevens informatie verzameld omtrent het optreden van een skala aan prenarkotische klachten "tijdens of vlak na het werk". Prenarkotische klachten kunnen een weerspiegeling zijn van de akute neurotoxische effecten van organische oplosmiddelen. Uit Tabel 3 blijkt dat de geëxponeerde controlepersonen significant vaker positief scoren op een drietal klachten, te weten: "misselijk gevoel", "kortademigheid" en "gebrek aan eetlust". Kenmerkend voor prenarkotische klachten is dat de klachten snel verdwijnen als de expositie aan organische oplosmiddelen verdwijnt. Van de geëxponeerde controles geeft 13,2% een vermindering van de klachten aan tijdens het weekend of vakantie, voor de niet-geëxponeerden bedraagt dit percentage 7,4%. Dit statistisch significante verschil suggereert dat de door de

blootgestelde controles gerapporteerde prenarkotische klachten ook in werkelijkheid samenhangen met de blootstelling aan organische oplosmiddelen. Binnen de blootgestelde controlepopulatie is géén korrelatie gevonden tussen de neurasthene klachtenrapportage en de diverse expositie-indices. Een korrelatie was wel aanwezig tussen de prenarkotische (akute) klachtenrapportage en de schilders- en algemene expositie-index. Opvallend was tenslotte de korrelatie die binnen de blootgestelde en niet-blootgestelde controlegroep bestond tussen werkstress en prenarkotische en neurasthene klachtenrapportage.

4. Neurosen

In het voorafgaande is gesuggereerd dat er een relatie bestaat tussen blootstelling aan organische oplosmiddelen en neurosen. Een aanvullend onderzoek met behulp van informatie uit de vragenlijsten bracht géén aanwijzingen aan het licht die het bestaan van een kausale relatie tussen blootstelling aan organische oplosmiddelen en het ontwikkelen van neurosen ondersteunen. De blootstelling van cases met "neurosen" bleek niet hoger en/of intensiever te zijn geweest dan de blootstelling van cases gediagnostiseerd met andere psychische aandoeningen. De gerapporteerde klachten van de cases met neurosen waren niet meer in overeenstemming met de klachten die volgens de literatuur bij het organic solvent syndroom passen⁴, dan de gerapporteerde klachten van cases met andere psychische aandoeningen.

BIAS

Bij de interpretatie van de onderzoeksresultaten is het noodzakelijk aandacht te besteden aan de bias (vertekening), welke in dit onderzoek een rol kan hebben gespeeld. Sturmans⁶ onderscheidt twee belangrijke vormen van bias: selectie bias en informatie bias. Selectie bias kan zijn opgetreden als de niet in het onderzoek betrokken groep (weigeraars, telefonisch niet bereikbare personen) kwa blootstelling en/of diagnosecodes verschilt van de wel in het onderzoek betrokken groep. Van de niet in het onderzoek betrokken cases en controles is bekend bij welk sociaal fonds (SFS of SFB) ze zijn aangesloten. Tevens is van de cases de ICD-kode bekend. Op grond van deze gegevens kon worden gekonkludeerd dat met

betrekking tot deze twee factoren (sociale fondsen en ICD-kodes) géén belangrijke selectie bias was opgetreden.

Een andere potentiële bron van selectie bias wordt mogelijk gevormd door de toekenning van diagnoses door de verzekeringsarts aan de patiënten. Hoofdgroep V, psychische aandoeningen, vormt een moeilijk diagnostisch terrein. Zo zal bijvoorbeeld bij een reactief beeld tengevolge van "stress" een keuze moeten worden gemaakt tussen ICD 300 (neurosen) en ICD 309 (situatieve of exogene reactie). De vraag of men met een "normale" of een "neurotische" reactie op stress te maken heeft, zal niet door alle verzekeringsartsen op dezelfde wijze worden beantwoord. Bedacht dient echter te worden dat schilders én bouwvakkers zijn gezien door de artsen van één medische dienst, zodat deze misklassifikatie de blootgestelden en de niet-blootgestelden in gelijke mate treffen.

Arbeidsmarktfactoren kunnen ook een rol spelen in het risico op WAO-intrede. Met name oudere en werkloze werknemers komen soms ten onrechte (?) in de WAO terecht. Deze situatie speelde vooral in de zeventiger jaren, maar de aanwezigheid van deze arbeidsmarktfactoren tijdens de onderzoeksperiode (april 1984 - april 1986) kan zeker niet worden uitgesloten. Deze vorm van bias zal echter zowel bij de blootgestelden als bij de niet-blootgestelden zijn opgetreden. Het vinden van verbanden tussen blootstelling aan oplosmiddelen en psychische aandoeningen zal door dit soort factoren echter worden bemoeilijkt.

In een onderzoek waarbij door middel van vragenlijsten informatie wordt verzameld, moet altijd rekening worden gehouden met het optreden van informatie bias. Bovendien is in Nederland in 1984 via een perskonferentie meer bekendheid gegeven aan de relatie tussen psychische aandoeningen en blootstelling aan organische oplosmiddelen. Een vorm van informatie bias, waarbij schilders die op de hoogte zijn van deze relatie geneigd zijn om meer klachten aan te geven, is dus niet uitgesloten.

BESCHOUWING EN KONKLUSIES

Het risico dat schilders in vergelijking met andere bouwvakkers lopen op WAO-intrede tengevolge van psychische aandoeningen, is ook na correctie voor verstoringe variabelen niet statistisch significant verhoogd (OR = 1,17). De onderzoekers zijn echter van mening dat op basis van de resultaten van dit onderzoek niet zonder meer gesproken kan worden van een negatieve studie. Deze konklusie is

gebaseerd op de gevonden positieve trends voor diverse dosis-respons relaties. Tevens is een verhoogd risico op WAO-intrede tengevolge van psychische aandoeningen gekonstateerd voor schilders die door de aard van hun werkzaamheden aan hoge concentraties organische oplosmiddelen blootstaan (bijv. werken in slecht geventileerde ruimten, werken met afbijtmiddelen). Een verdeling van de hoofdgroep "psychische aandoeningen" in verschillende diagnosegroepen brengt aan het licht dat de diagnose "neurosen" (ICD 300) vaker bij schilders als diagnose wordt gebruikt (OR = 2,3). De diagnose "situatieve of exogene reactie" (ICD 309) die niet scherp te onderscheiden is van de diagnose "neurosen" wordt echter minder vaak aan schilders toegekend, terwijl de combinatie van beide diagnosecodes geen verhoogd risico voor schilders laat zien. Het is dan ook mogelijk dat de gevonden associatie tussen blootstelling aan organische oplosmiddelen en "neurosen" het gevolg is van een klassifikatie-artefact.

Alhoewel het bestaan van een (licht) verhoogd risico op WAO-intrede tengevolge van psychische aandoeningen op grond van deze onderzoeksresultaten niet uitgesloten kan worden, zijn de gevonden associaties in ieder geval zwakker dan uit overeenkomstig Scandinavisch onderzoek naar voren komt⁷⁻⁹. Als er al sprake is van een verhoogd risico bij schilders op neurotoxische effecten die tot WAO-intrede leiden, dan is het verhoogde risico beperkt tot de (kleine) groep schilders met de hoogste blootstelling aan organische oplosmiddelen.

Naast de overeenkomsten in onderzoeksopzet met de Scandinavische onderzoeken, zijn echter ook enkele verschillen te noemen:

- Het gebruik van een andere ICD-kodering voor de cases (ICD-9 versus ICD-8);
- Verschillen tussen Nederland en Scandinavië met betrekking tot de criteria voor het toekennen van een arbeidsongeschiktheidsuitkering;
- De keuze van een andere controlegroep (gezonden versus arbeidsongeschikten).

Bovendien bestaat de mogelijkheid dat de Scandinavische schilders in het verleden aan hogere concentraties oplosmiddelen blootgesteld zijn geweest dan hun Nederlandse kollega's¹⁰.

Tenslotte komt uit dit onderzoek naar voren dat onder blootgestelde werknemers uit de controlepopulatie het bestaan van akute (prenarkotische) klachten tengevolge van blootstelling aan organische oplosmiddelen duidelijker aantoonbaar is dan het optreden van chronische (neurasthene) klachten. Niet uitgesloten kan worden dat andere factoren (zoals bijv. werkstress) een belangrijke rol spelen in het ontstaan van deze klachten en in het mogelijk aanwezige licht verhoogde risico voor schilders op WAO-intrede door psychische aandoeningen.

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Het onderzoek dat in dit proefschrift wordt beschreven is tot stand gekomen en tot een goed einde gebracht dankzij de medewerking van een groot aantal personen en enkele stichtingen:

- De Stichting Arbouw heeft de uitvoering van dit onderzoek gesubsidieerd. Daarnaast hebben de heren van Duivenbouden, Koningsveld en Ligteringen een actieve rol gespeeld in de begeleiding van het onderzoek.
- De Stichting Sociaal Fonds Schildersbedrijf (SFS) en de Stichting Sociaal Fonds Bouwnijverheid (SFB) hebben door middel van hun coöperatieve opstelling een essentiële bijdrage geleverd aan de realisatie van dit onderzoek. De heren Vergers, Visser en de Kieviet van het SFB en de heren Mos, Quint en Zweerts van het SFS wil ik op deze plaats met name noemen.
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Het noemen van namen brengt altijd het risico met zich mee dat een aantal personen ten onrechte niet worden genoemd. Als u tot deze vergeten categorie mocht behoren, bied ik u bij voorbaat mijn oprechte excuses aan. Een promovendus is ook maar een feilbaar mens.

CURRICULUM VITAE

Volgens de Burgerlijke Stand ben ik op 11 juli 1959 te Noordwijkerhout geboren. Mijn middelbare schoolopleiding heb ik genoten op het Pieter Groen College te Katwijk, alwaar ik in juni 1977 het VWO-diploma behaalde. In september 1977 begon ik met de studie Geneeskunde aan de Rijksuniversiteit Leiden (= RUL). Na het kandidaatsexamen (juni 1980) en het doktoraalexamen (oktober 1982) volgde de periode van senior co-assistentschappen. In mei 1984 werd deze periode afgesloten met het behalen van het artsexamen (cum laude). Gedurende de periode september 1984 tot en met januari 1985 ben ik werkzaam geweest bij de Rijks Geneeskundige Dienst (thans: Rijks Bedrijfsgezondheids- en Bedrijfsveiligheids Dienst), Hoofdafdeling Medische Zaken te Den Haag. In het kader van een arbeidservaringsproject hield ik mij bezig met de standaardisatie en operationalisering van de histamine-provokatietest. Mijn werkzaamheden bij de Vakgroep Arbeidsgeneeskunde, Milieugezondheidkunde en Toxicologie (AMT) van de Rijksuniversiteit Limburg (= RL), aanvankelijk als wetenschappelijk assistent en later als universitair docent, vingen aan in februari 1985.

De uitvoering van het in deze dissertatie beschreven onderzoek vormde een belangrijk onderdeel van mijn werkzaamheden. Andere onderzoeksactiviteiten lagen op het terrein van "Arbeid en Gezondheid", met een duidelijk accent op de arbeidsepide-miologie. Daarnaast participeerde ik in het onderwijs aan studenten van de Facul-teit der Geneeskunde en de Faculteit der Gezondheidswetenschappen.

In januari 1985 ben ik begonnen met de vierjarige opleiding tot sociaal-genees-kundige, tak arbeids- en bedrijfsgeneeskunde, door middel van een medewerkerschap aan een universiteit (i.c. de Vakgroep AMT van de RL).

APPENDICES

Appendix 1: List of Three-digit Categories of mental disorders (ICD-9)

Appendix 2: Letter of introduction

Appendix 3: Letter accompanying the questionnaire

Appendix 4: Questionnaire

APPENDIX 1: LIST OF THREE-DIGIT CATEGORIES OF MENTAL DISORDERS (ICD-9)

MENTAL DISORDERS

Organic psychotic conditions (290-294)

- 290* Senile and presenile organic psychotic conditions
- 291 Alcoholic psychoses
- 292 Drug psychoses
- 293 Transient organic psychotic conditions
- 294 Other organic psychotic conditions (chronic)

Other psychoses (295-299)

- 295* Schizophrenic psychoses
- 296* Affective psychoses
- 297 Paranoid states
- 298* Other nonorganic psychoses
- 299 Psychoses with origin specific to childhood

Neurotic disorders, personality disorders and other nonpsychotic mental disorders (300-316)

- 300* Neurotic disorders
- 301* Personality disorders
- 302 Sexual deviations and disorders
- 303* Alcohol dependence syndrome
- 304* Drug dependence
- 305 Nondependent abuse of drugs
- 306* Physiological malfunction arising from mental factors
- 307* Special symptoms or syndromes not elsewhere classified
- 308 Acute reaction to stress
- 309* Adjustment reaction
- 310* Specific nonpsychotic mental disorders following organic brain damage
- 311* Depressive disorder, not elsewhere classified
- 312* Disturbance of conduct not elsewhere classified
- 313 Disturbance of emotions specific to childhood and adolescence
- 314 Hyperkinetic syndrome of childhood
- 315 Specific delays in development
- 316 Psychic factors associated with diseases classified elsewhere

Mental retardation (317-319)

- 317* Mild mental retardation
 - 318* Other specified mental retardation
 - 319 Unspecified mental retardation
-

* ICD-codes included in the list of diagnostic codes as operated by the federation of Dutch industrial insurance boards.

APPENDIX 2: LETTER OF INTRODUCTION

Dear Sir,

The University of Limburg, in collaboration with the Dutch Organization for the Improvement of Working Conditions in the Construction Industry (Stichting Arbeid), intends to carry out an investigation regarding health and working conditions among painters and construction workers.

Persons receiving disability benefits, previously working as painter or construction worker, will also be included in this study. The objective of this project is to investigate relationships between working conditions among painters and construction workers and the development of health complaints.

Since you are or have been working as construction worker or painter, we request you to participate in this study. If you are willing to participate in this study, you will be sent a questionnaire. This questionnaire includes items about your education, (former) occupations and health conditions. Altogether it will take 30 to 60 minutes to answer all the questions.

In a few days you will be contacted by telephone by an employee of the University of Limburg to hear if you are willing to participate in the study. Self-evidently carefulness and privacy protection will be maintained at the processing of your data. At the university your name will only be known to the undersigned and my immediate colleague. The questionnaires will be anonymised, so your name can not be mentioned in the reporting of the data.

Thanking you in advance for your cooperation.

Yours faithfully,

C. van Vliet, physician
Department of Occupational Medicine
University of Limburg
Maastricht

APPENDIX 3: LETTER ACCOMPANYING THE QUESTIONNAIRE

Dear Sir,

Herewith you receive, as agreed by telephone, a questionnaire for the project: "Health and working conditions among painters and construction workers". The investigation is carried out by the University of Limburg, in collaboration with the Dutch Organization for the Improvement of Working Conditions in the Construction Industry (Stichting Arbouw).

The questionnaire includes items about your education, the occupations you have practised and your health conditions. Most questions can be answered by marking the fixed round corresponding to your choice of the given answers of the relevant question. For some other questions you are requested to write down your answer. Read all questions carefully and take your time for completing the questionnaire. It is very important that you completely answer all questions referring to you. If you are in doubt about the meaning of a question, please contact the undersigned. You can return the questionnaire in the enclosed prepostaged envelope.

Thanking you in advance for your co-operation.

Yours faithfully,

C. van Vliet, physician
Department of Occupational Medicine
University of Limburg
Maastricht

APPENDIX 4: QUESTIONNAIRE

1) What is your age?

..... years.

2) What is your current marital status?

- ☐ Single
- ☐ Living together
- ☐ Married
- ☐ Divorced
- ☐ Widower

3) Do you receive disability benefits?

- ☐ Yes
- ☐ No

If so, since when?

19....

THE QUESTIONS 4, 5 AND 6 NEED ONLY TO BE ANSWERED IF YOU RECEIVE DISABILITY BENEFITS. IF YOU DO NOT RECEIVE DISABILITY BENEFITS, YOU MAY CONTINUE TO QUESTION NUMBER 7.

4) For what percentage are you disabled at the moment?

☐ Less than 15%	☐ 55/65%
☐ 15/25%	☐ 65/80%
☐ 25/35%	☐ 80/100%
☐ 35/45%	☐ I do not know
☐ 45/55%	

5) By which cause or disease have you become disabled?

- ☐
-

6) Do you think that working conditions have contributed to your disability for work?

- ☐ Yes
- ☐ No
- ☐ I do not know

If yes, which working conditions?

.....

NEXT SOME QUESTIONS ARE ASKED ABOUT YOUR EDUCATION.

7) Have you finished primary school?

☐ Yes

☐ No

8) Have you ever failed a year in primary school?

☐ Yes

☐ No

9) Have you, after primary school, taken and/or finished one or more of the following educations?

	Followed	Finished (diploma)
- Junior secondary technical school	☐	☐
- Senior secondary technical school	☐	☐
- School for lower general secondary education	☐	☐
- Pre-university education	☐	☐
- Higher vocational education	☐	☐
- University	☐	☐
- Other schools or educations:		
.....		☐
.....		☐
.....		☐

NEXT SOME QUESTIONS ARE ASKED ABOUT YOUR OCCUPATION.

10) Have you ever practiced the following occupations?

If yes, how many years?

	Yes	No	Number of years
- Brick layer	☐	☐	
- Carpenter	☐	☐	
- Tiler	☐	☐	
- Painter	☐	☐	
- Plasterer	☐	☐	
- Hodman	☐	☐	

- Carpet layer	0	0	
- Engineer	0	0	
- Road marker	0	0	
- Ground worker	0	0	
- Asphalt worker	0	0	
- Other trades:			
.....			
.....			
.....			
.....			

11) Have you ever been unemployed?

☐ Yes

☐ No

If yes, when was your latest unemployment period?

From 19.. to 19..

THE QUESTIONS 12 TO 24 NEED ONLY TO BE ANSWERED BY YOU IF YOU EVER WORKED AS A PAINTER. IF YOU HAVE NEVER WORKED AS PAINTER, YOU MAY CONTINUE TO QUESTION NUMBER 25.

12) In what year did you start working as a painter?

19..

13) How many years have you worked as a painter?

..... years

14) Have you been unemployed and/or ill for more than one year during this period?

☐ Yes

☐ No

If yes, how many years?

..... years

15)	Yes	No	Number of years
- Have you worked in maintenance painting?	0	0	
If yes, how many years?			
- Have you worked in newbuilding painting?	0	0	
If yes, how many years?			

- Have you worked in construction painting? 0 0
 If yes, how many years?
- Did you do other painting work? 0 0

IN THE QUESTIONS 16 TO 24 A DISTINCTION IS MADE BETWEEN YOUR WORKING ACTIVITIES AND WORKING CONDITIONS "DURING THE PAST YEAR" AND "PREVIOUSLY". IF YOU ARE CURRENTLY NOT WORKING AS A PAINTER (E.G. BECAUSE YOU ARE DISABLED OR NOW PRACTICE ANOTHER OCCUPATION), YOU SHOULD CONSIDER "DURING THE PAST YEAR" AS YOUR LAST WORK YEAR AS PAINTER AND "PREVIOUSLY" AS THE PRECEDING YEARS.

- 16) How many hours a week have you worked during the past years?
 hours a week

And previously?

- ☐ Just as many hours a week
☐ Fewer hours a week
☐ More hours a week

- 17) Last year, how many hours did you spend painting in your spare time at your own house or for others?
 hours a week

And previously?

- ☐ Just as many hours a week
☐ Fewer hours a week
☐ More hours a week

- 18) Last year, what percentage of your time did you spend on other activities than painting (e.g. preparation, wall papering, filling, sanding etc.)?
☐ 0 - 10%
☐ 10 - 20%
☐ 20 - 30%
☐ More than 30%

And previously?

- ☐ As much time
☐ Less time
☐ More time

19) Last year, how often have you worked with the following paints?

	Never or almost never	One day a week	2 or 3 days a week	4 or more days a week
- Latex	0	0	0	0
- Alkyd	0	0	0	0
- Epoxy	0	0	0	0
- Others,				
.....	0	0	0	0
.....	0	0	0	0

And previously?

	Never or almost never	One day a week	2 or 3 days a week	4 or more days a week
- Latex	0	0	0	0
- Alkyd	0	0	0	0
- Epoxy	0	0	0	0
- Others,				
.....	0	0	0	0
.....	0	0	0	0

20) Last year, with what equipment did you paint?

	Never or almost never	One day a week	2 or 3 days a week	4 or more days a week
Paint brush	0	0	0	0
Paint roller/sweeper	0	0	0	0
Paint spray	0	0	0	0

And previously?

	Never or almost never	One day a week	2 or 3 days a week	4 or more days a week
Paint brush	0	0	0	0
Paint roller/sweeper	0	0	0	0
Paint spray	0	0	0	0

21) Last year, which paint trademark did you use mostly?

.....

And previously?

.....

22) Last year, how often did you perform the following activities?

	Never or almost never	One day a week	2 or 3 days a week	4 or more days a week
- Scouring off old paint coats	0	0	0	0
- Burning off old paint coats	0	0	0	0
- Stripping old paint coats	0	0	0	0

And previously?

	Never or almost never	One day a week	2 or 3 days a week	4 or more days a week
- Scouring off old paint coats	0	0	0	0
- Burning off old paint coats	0	0	0	0
- Stripping old paint coats	0	0	0	0

23) Last year, did you use a respirator?

- ☐ Never or almost never
- ☐ One day a week
- ☐ Two or three days a week
- ☐ Four or more days a week

And previously?

- ☐ Never or almost never
- ☐ One day a week
- ☐ Two or three days a week
- ☐ Four or more days a week

24) Which description corresponds best to your working conditions during the past year?

- ☐ Generally inside, small rooms, well ventilated
- ☐ Generally inside, small rooms, poorly ventilated
- ☐ Generally inside, large rooms, well ventilated
- ☐ Generally inside, large rooms, poorly ventilated
- ☐ Generally outside
- ☐ Otherwise,

And previously?

- O Generally inside, small rooms, well ventilated
- O Generally inside, small rooms, poorly ventilated
- O Generally inside, large rooms, well ventilated
- O Generally inside, large rooms, poorly ventilated
- O Generally outside
- O Otherwise,

NEXT QUESTIONS MUST BE ANSWERED BY EVERYONE

IN THE QUESTIONS 25 AND 26 A DISTINCTION IS MADE BETWEEN YOUR WORK ACTIVITIES AND WORKING CONDITIONS "DURING THE PAST YEAR" AND "PREVIOUSLY". IF YOU ARE CURRENTLY NOT WORKING (E.G. BECAUSE YOU ARE UNEMPLOYED OR DISABLED) YOU SHOULD CONSIDER "DURING THE PAST YEAR" AS YOUR LAST WORK YEAR AND "PREVIOUSLY" AS THE PRECEDING YEARS.

25) Last year, did you do your work in one room with:

	Never or almost never	One day a week	2 or 3 days a week	4 or more days a week
- Painters	0	0	0	0
- Carpetlayers	0	0	0	0

And previously?

	Never or almost never	One day a week	2 or 3 days a week	4 or more days a week
- Painters	0	0	0	0
- Carpetlayers	0	0	0	0

26) Last year, did you use during your work:

	Never or almost never	One day a week	2 or 3 days a week	4 or more days a week
- Paint removers	0	0	0	0
- Solvents (such as White spririts)	0	0	0	0
- Glues	0	0	0	0
- Degreasing agents	0	0	0	0

And previously?

	Never or almost never	One day a week	2 or 3 days a week	4 or more days a week
- Paint removers	0	0	0	0
- Solvents (such as White Spirits)	0	0	0	0
- Glues	0	0	0	0
- Degreasing agents	0	0	0	0

NEXT QUESTION REFERS TO THE PAST (WORK)YEAR. IF YOU ARE CURRENTLY NOT WORKING, YOU SHOULD CONSIDER THE PAST YEAR AS YOUR LAST WORK YEAR. YOU CAN CHOOSE FROM FOUR ANSWERS:

- NEVER
- SOMETIMES (ONCE A MONTH)
- REGULAR (ONCE A WEEK)
- OFTEN (MORE THAN ONCE A WEEK)

27) During or right after my work I suffer from:

	Never	Sometimes	Regular	Often
- Nausea	0	0	0	0
- Vomiting	0	0	0	0
- Dizziness	0	0	0	0
- Drunken feeling	0	0	0	0
- Headache	0	0	0	0
- Shortness of breath	0	0	0	0
- Absent mindedness	0	0	0	0
- Misunderstanding of instructions and work assignments	0	0	0	0
- Ear tingling	0	0	0	0
- Difficulties with talking	0	0	0	0
- Loss of appetite	0	0	0	0
- Drowsiness	0	0	0	0
- Alcohol intolerance	0	0	0	0

28) If you marked once or more times "often" at the preceding question, did you notice a decrease of your complaint(s) during the weekends or holidays?

- 0 Yes
- 0 No

SUBSEQUENTLY A NUMBER OF QUESTIONS ARE ASKED ABOUT YOUR HEALTH CONDITIONS.

- 29) Have you ever been treated by a physician for one or more of the diseases or disorders mentioned below? Please, indicate the year of first treatment and whether or not you are still treated for that disease/disorder.

	Yes	No	Year	Still treated	
				Yes	No
- Diabetes	0	0		0	0
- High blood pressure	0	0		0	0
- Heart disease (e.g. heart attack)	0	0		0	0
- Vascular disease (e.g. thrombosis)	0	0		0	0
- Overweight	0	0		0	0
- Sleeplessness	0	0		0	0
- Overstrained	0	0		0	0
- Epilepsy	0	0		0	0
- Skin disease	0	0		0	0
- Bronchitis or asthma	0	0		0	0
- Rheumatism	0	0		0	0
- Muscle or joint complaints	0	0		0	0
- Neck or back complaints	0	0		0	0
- Stomach	0	0		0	0
- Gall-bladder	0	0		0	0
- Kidneys or bladder	0	0		0	0
- Accident	0	0		0	0
- Concussion	0	0		0	0
- Thyroid gland disease	0	0		0	0
- Other disease/complaint	0	0			
If yes, which disease?					
.....				0	0

- 30) Suffer or suffered any of your next of kin (parents, brothers, sisters) from dementia?

0 Yes
0 No

- 31) Have you ever been operated?

0 Yes
0 No

If yes, what for and when?

1.
2.
3.

32) Have you ever been unconscious?

☐ Yes

☐ No

If yes, cause :
 duration:
 when :

33) Do you use medication?

☐ Yes

☐ No

If yes, which medication?

.....

NEXT QUESTION DEALS WITH A NUMBER OF SYMPTOMS WHICH YOU MAY OR MAY NOT HAVE EXPERIENCED YOURSELF. YOU CAN CHOOSE FROM FOUR ANSWERS:

- NEVER
- SOMETIMES (ONE A MONTH)
- REGULAR (ONCE A WEEK)
- OFTEN (MORE THAN ONCE A WEEK)

PLEASE CONSIDER YOUR HEALTH CONDITIONS AS EXPERIENCED DURING THE LAST MONTH.

34)	Never	Sometimes	Regular	Often
- Do you get up tired in the morning?	0	0	0	0
- Do you feel excess tiredness after the workday?	0	0	0	0
- Are you forgetful?	0	0	0	0
- Do you often forget what you intend to do?	0	0	0	0
- Do you have to go back and check whether you turned of the gas, locked the door etc.?	0	0	0	0

- Do you make notes of things you must remember?	0	0	0	0
- Do your thoughts stray when you try to concentrate?	0	0	0	0
- Do you fall asleep when watching television?	0	0	0	0
- Are you lost in your own thoughts?	0	0	0	0
- Do you notice that you are "day-dreaming"?	0	0	0	0
- Do you have difficulties understanding what you read in newspapers or books?	0	0	0	0
- Do you have difficulties falling asleep?	0	0	0	0
- Do you wake up at night?	0	0	0	0
- Do you have nightmares?	0	0	0	0
- Does your mood change without reason?	0	0	0	0
- Are you depressed?	0	0	0	0
- Are you irritated?	0	0	0	0
- Are you restless?	0	0	0	0
- Are you afraid?	0	0	0	0
- Are you listless?	0	0	0	0
- Are you drowsy?	0	0	0	0
- Do you become tired among other people?	0	0	0	0
- Do you have difficulties in starting a conversation with others?	0	0	0	0
- Do you suffer from headaches?	0	0	0	0
- Do you suffer from dizziness?	0	0	0	0
- Do you sweat without exerting yourself?	0	0	0	0
- Do you have palpitations without exerting yourself?	0	0	0	0
- Do your hands tremble?	0	0	0	0
- Do you feel as though you have something in your throat?	0	0	0	0
- Do you feel an oppression on your chest?	0	0	0	0
- Do you suffer from a diminished sexual interest?	0	0	0	0
- Do your legs feel numb or tingle?	0	0	0	0

35) What is your length? cm
And your weight? kg

36) Do you drink alcoholics (bear, gin, wine etc.)?
☐ Yes
☐ No
If yes, how many drinks a week?
☐ Less than 10
☐ 10 to 25
☐ 25 to 50
☐ More than 50

37) Do you smoke or have you smoked?
☐ Yes
☐ No
If yes, how many cigarettes a day?
☐ Less than 10
☐ 10 to 20
☐ More than 20
How long do or did you smoke?
☐ Shorter than 1 year
☐ 1 to 5 years
☐ 5 to 10 years
☐ 10 to 20 years
☐ Longer than 20 years
Do you still smoke?
☐ Yes
☐ No

38) Did you have serious private problems during the last year?
☐ Yes
☐ No

39) Which hobbies do you have?
.....

FINALLY, A NUMBER OF QUESTIONS ARE ASKED ABOUT YOUR LATEST OCCUPATION?

- 40) Did you carry out your activities under pressure of time (piece work system)?
☐ Yes
☐ No
- 41) Did you get on well with your colleagues?
☐ Yes
☐ No
- 42) Where there serious conflicts on your work?
☐ Yes
☐ No
- 43) Did you enjoy going to your work?
☐ Yes
☐ No
- 44) Do you want to inform us of matters that have not been raised in this questionnaire?
☐ Yes
☐ No
If yes, what matters?

YOU HAVE COME AT THE END OF THIS QUESTIONNAIRE. PLEASE CHECK WHETHER YOU HAVE ANSWERED COMPLETELY ALL RELEVANT QUESTIONS.

FINALLY, WE WISH TO THANK YOU AGAIN FOR YOUR PARTICIPATION IN THIS INVESTIGATION!