A Review of the Literature Relating to the Chronic Neurobehavioural Effects of Occupational Exposure to Organic Solvents

Dr Anne Spurgeon
Institute of Occupational Health
University of Birmingham

September 2002

Contents

Report Structure

This report is divided into six sections

Section I: Objectives and Scope

This section contains a brief introduction to the subject together with the objectives of the review developed within the context of the requirements of IIAC. It also defines the scope of the literature to be covered

Section II: Methodology

This section contains a description of the search methodology and the results in numerical terms

Sections III, IV and V contain evaluations of the data relating to three areas of investigation. A summary is included at the end of each section

Section III: Studies using neurobehavioural tests

Section IV: Studies using symptom questionnaires

Section V: Cohort and case-referent studies

Section VI: Executive Summary and Conclusions

This section contains a summary evaluation of the data and conclusions in relation to each of the objectives specified in Section I

Appendices

Appendix I contains a description of each of the databases used in the search.

Appendix II consists of Tables I – VII. These tables contain details of the studies discussed in sections III, IV and V

Section I

Objectives and Scope

Introduction

Concerns that exposure to organic solvents in the workplace may cause irreversible damage to the central nervous system arose during the 1970s. The acute, reversible effects of such exposure were already well-accepted and largely understood. However the new concerns focussed on the potential for chronic irreversible effects to occurring a result of long-term (years) of exposure at levels which might or might not be sufficient to cause acute effects.

A substantial scientific literature has developed in this field during the last 30 years. However the subject remains controversial with a lack of consensus on many fundamental issues. This report constitutes a review and evaluation of the available literature and the current scientific position in this field. It is intended to provide information to IIAC as a basis for their considerations on whether the effects of occupational exposure to organic solvents should be recommended for inclusion in the UK list of prescribed diseases.

Objectives of the Review

The legal requirements for prescription set out in the IIAC Report, Conditions due to Chemical Agents (2002) indicate that the current review should attempt to encompass the following areas in so far as they are contained in the literature:

(i) a workable definition of the disease.

This requires information on the existence, nature and size of effects on the nervous system which can result from long-term occupational exposure to organic solvents, as well as information on valid reliable methods of assessment and diagnosis.

(ii) attribution to occupational exposure.

This requires information on the level and duration of solvent exposure likely to produce those effects.

(iii) where the disease is indistinguishable from one with other non-occupational causes, evidence of an increased risk in certain occupational situations.

This requires information on the rate of occurrence of the disease, as defined, in certain occupational groups where exposure to organic solvents is known to occur.

Given the above requirements the objectives of the review are defined as follows:-

(i) to determine whether the existing literature provides evidence that occupational exposure to organic solvents can result in chronic adverse effects on cognitive functioning or the development of psychiatric disorders.

(ii) to determine whether the size and nature of any identified chronic adverse effects, together with valid and reliable methods of assessment, can be defined from the current literature.

(iii) to determine whether the duration and level of exposure associated with any identified chronic adverse effects can be determined from the current literature.

(iv) to determine whether, from the current literature, it is possible to determine the size of the risk of developing chronic adverse effects on cognitive functioning or psychiatric disorders associated with long-term occupational exposure to organic solvents.

Literature Scope

The study of neurotoxicity encompasses a number of different elements which may be broadly classified as (i) structural toxicity, concerned with responses of the neurones and supporting cells, (ii) biochemical toxicity concerned with metabolic changes and (iii)

functional toxicity which focuses on aspects of behaviour and the experience of health and well-being. While all these aspects may be included in the definition of a disease process, human investigations of the chronic neurotoxic effects of solvent exposure have predominantly focussed on (iii) functional toxicity. Thus the overwhelming majority of studies in this field are in the form of epidemiological investigations of working populations which report outcomes based on the results of neurobehavioural (cognitive performance) tests and reports of neuropsychiatric symptoms. A smaller literature has been concerned with structural toxicity focussing on neurophysiological tests such as nerve conduction and various forms of brain imaging. Studies in the field of biochemical toxicity tend to be concerned with the study of specific compounds rather than on the solvent mixtures usually encountered in working situations.

The current review is essentially concerned with functional toxicity and will therefore be confined to studies involving neurobehavioural outcomes and symptom reporting. For reference however it is noted that the literature concerning outcomes related to structural toxicity (neuroimaging, neurophysiology and histopathology) has recently been reviewed for the Health and Safety Executive, (Ridgway, 2002).

Most publications in this field refer to epidemiological studies which report outcomes based on levels of functioning rather than on specific conditions. However the literature also contains studies of patient groups, including case series and follow-up investigations. These studies are primarily concerned with the nature of the condition known as Chronic Toxic Encephalopathy (CTE) which in many countries is regarded as the disease end-point following long-term solvent exposure. The assessment and diagnosis of CTE is largely in terms of performance on neurobehavioural tests and symptom reporting and these studies are

therefore included in the current review, together with papers which discuss diagnostic criteria.

In addition a number of studies have been carried out which investigate the occurrence of nervous system conditions notably certain psychiatric disorders, non-specified dementia and Alzheimer's disease in those employed in occupations involving solvent exposure. Since diagnosis of these conditions is also primarily in terms of behavioural outcomes and symptomatology these studies will also be included.

The main sources of information on solvent exposure levels and duration associated with neurotoxic effects are the epidemiological studies. However some information on these aspects is also contained in studies of patient groups and is discussed in relation to the diagnostic criteria for CTE. It should be noted that all studies included here refer to mixed exposures and cannot therefore provide information on the effects of exposure to specific substances, although the substances contained in the mixtures are often recorded. Exposure to solvent mixtures represents by far the most common occupational experience in these workers, such that it is rarely possible to discriminate between the effects of different compounds.

A summary of the field of literature encompassed by the review is therefore as follows:

- reports of studies of active solvent-exposed workers which include outcomes based on the results of (i) neurobehavioural tests (ii) symptomatology, including psychiatric diagnosis
- reports of case series including studies involving groups of patients diagnosed with solvent-related disease compared with groups of non-patients
- reports of follow-up studies of patients

- reports of studies on the occurrence of certain types of nervous system disease in solvent-exposed workers
- papers which discuss diagnostic criteria for solvent-related disease.

Section II

Methodology

Literature Search

The following databases were identified as relevant to the subject of the report:

CISDOC
EMBASE
HSELINE
MEDLINE
NIOSHTIC
RILOSH
SCIENCE CITATION INDEX
SOCIAL SCIENCE CITATION INDEX

Details of these databases are included in Appendix I.

The literature search was carried out as follows:

Stage 1

Search terms
- neuropsychological tests
- neuropsychological
- neurobehavioural (neurobehavioral)
- behavioural (behavioral)
- behaviour (behavior)
- cognition disorders

the results of all search terms in stage 1 were combined using the Boolean operator, **OR**

Stage 2

Search terms
- solvents
- paints
- ink
- varnish
- printers
- glue
- organic solvent
- organic solvent syndrome

the results of all search terms in stage 2 were combined using the Boolean operator, **OR**

Stage 3
The results of all search terms from stage 1 and stage 2 were combined using the Boolean operator, **AND**

The following limitations were placed on the results from stage 3

Limitations	human
	English language
	1970-2002
	[N.B. Science Citation Index, Social Science Citation Index, Arts and Humanities Citation Index from 1981-2002]

Stage 4

Search terms	neuropsychiatric
	anxiety
	depression

the results of all search terms in stage 4 were combined using the Boolean operator, **OR**

Stage 5

Search terms	solvents
	paints
	ink
	varnish
	printers
	glue
	organic solvent
	organic solvent syndrome

the results of all search terms in stage 5 were combined using the Boolean operator, **OR**

Stage 6
The results of all search terms from stage 4 and stage 5 were combined using the Boolean operator, **AND**

The following limitations were placed on the results from stage 6

Limitations	human
	English language
	1970-2002
	[N.B. Science Citation Index, Social Science Citation Index, Arts and Humanities Citation Index from 1981-2002]

Stage 7
The results of all search terms from stage 6 were combined with the results from stage 3 using the Boolean operator, **NOT** to exclude any duplicate records.

Initial search results

The original search produced a total of 206 papers. The following selection and exclusion criteria were then applied to select papers relevant to the review.

Initial selection criteria

- Papers reporting on investigations of the neurobehavioural and mental health effects of exposure to organic solvents
- Papers reporting on diagnostic criteria for solvent-related health effects

Exclusion criteria

- Investigations of short-term exposure and/or acute effects
- Investigations of non-occupational exposure
- Investigations of single substances
- Investigations involving neurophysiological, or neuropathological measures
- Investigations involving specific sensory outcomes (hearing and colour vision)
- Animal studies
- Test development studies
- Single case studies
- Review papers (used only to check on references)

Final search results

Following application of selection and inclusion criteria the following papers were identified:

- 58 papers were identified which reported on investigations of active workers that involved neurobehavioural testing. Details are provided in Tables I (methodology) and II (outcomes).

- 55 papers were identified which reported on investigations of symptomatology in active workers. Of these, 39 reported on symptomatology alongside test results in the neurobehavioural investigations noted above. Details of these 39 studies are also shown in Table I (methodology) therefore, with additional details in Table III (outcomes)

  A further 16 papers reported on symptomatology alone (no neurobehavioural tests). Details of these are shown in Table IV
- 3 papers were identified as providing investigation or discussion of diagnostic criteria
- 18 papers were identified as reporting on case series. Details of these are shown in Table V
- 9 papers were identified which report on the follow-up of patients diagnosed with solvent-related conditions. Details of these are shown in Table VI
- 19 papers were identified which report on cohort or case-referent studies. Details of these are shown in Table VII

Tables I – VII are contained in Appendix II.

Section III

Studies using Neurobehavioural Tests (Refer to Tables I & II)

Study Characteristics

A total of 58 studies were identified which used neurobehavioural tests to investigate the effects of long-term occupational exposure to solvent mixtures. Details are shown in Tables I and II. With the exception of one study which investigated retired painters and aerospace workers (Daniell *et* al, 1999), all are concerned with active workers. The most common occupational groups studied were painters and paint makers which were included in 38 investigations. The first study was published in 1976 (Hanninen *et al*, 1976) and the most recent in 2002 (Nordling Nilson *et al*, 2002) with nineteen studies being published since 1995. Approximately two thirds of these were carried out either in Europe or the United States indicating no decrease in interest in this subject and no trend towards a majority of studies taking place in developing countries, where exposure levels are presumed to be higher. Only three studies have been carried out in the UK, the last in 1994 (Spurgeon *et al*, 1994).

The overwhelming majority of studies are cross-sectional in design. Most (47 studies) compare two groups of workers (exposed and non-exposed), although eight cross-sectional studies investigate a single group of workers using multivariate analysis to determine exposure-effect relationships while controlling for the effects of other variables. In total 41 studies include an analysis of exposure-effect as well as group comparisons. Approximately nine of these use duration (years) as the only basis for their index of exposure while the remainder have developed at least one cumulative index based on a combination of duration

and some estimation of exposure levels such as an analysis of historical monitoring data, job type or hygienist's assessment.

The inherent difficulties of cross-sectional studies, most notably the potential for bias resulting from the "healthy worker" or "survivor" effect, mean that data from longitudinal studies are generally preferred. However there are only four longitudinal studies in this dataset. Of these the study by Kilburn and Warshaw (1992) appears to be largely an exercise in determining the test re-test reliability of the tests rather than monitoring effects on workers. Differences in the composition of the study sample over time mean that the (negative) results of this study can be largely discounted for present purposes. The study by Williamson and Winder (1993) represented an attempt to gather baseline data on apprentice painters at the beginning of their employment, prior to future monitoring. Limited two year follow-up of (negative) cross-sectional results are presented. No further follow-up of this group has so far appeared in the published literature. The study by White *et al* (1995) similarly involved only a two year follow-up, although in this case the workers were printers with more than 10 years exposure. Results were largely negative both at original cross-sectional investigation and at follow-up. The final longitudinal study (Nordling Nilson *et al*, 2002) constitutes an 18 year follow-up of workers originally studied by Ekberg *et al* (1986) and represents the most useful study in the current context.

Outcome Measures

A very large number of different neurobehavioural tests have been used in these studies and this presents a number of problems in terms of comparing the results of different studies and thus reaching conclusions about the dataset as a whole.

Most obviously it is difficult to define exactly what is being measured in each case. Clearly different tests measure different aspects of cognitive functioning. However, it is rarely possible to group together different tests which purport to measure a particular function, since most such functions encompass a number of different elements. For example, the function of "memory" which is usually regarded as a prime target in studies of solvent exposure, includes a number of different aspects which different tests will address to different degrees (short and long term, auditory, visual, recognition, retrieval, cued recall, semantic, episodic etc). Further there is substantial overlap between different tests in terms of what they measure and considerable disagreement about this between investigators. As a further example, one of the most commonly used tests, the Symbol-Digit Substitution Test (SDST) is regarded by some investigators as a test of attention, by others as a test of paired-associate learning and by others as a general test of simple information processing.

The effects of attempting to interpret results by grouping tests in terms of the area of functioning they appear to measure is shown in Table 1 below. This classification is based on the author's own view of the primary functional area assessed by each test. Those which appear to assess a number of different areas are included in the "general" category.

Table 1
Use and results of neurobehavioural tests in 48 studies

Functional area	Frequency of tests employed (studies)	% showing positive effect
General	43	58
Memory (WAIS-R, WMS)	23	65
Memory (other)	63	40
Learning	28	39
Motor speed/control	50	30
Visuo-spatial organisation	41	56
Vigilance/attention	24	38
Reasoning	11	18
Reaction time	24	38

The data relate to the results of 48 neurobehavioural studies of solvent exposure carried out between 1976 and 1999 (data from Spurgeon, 2001). As such they represent the majority of studies contained in the current review. It is clear that there is little or no consistency or discernible pattern in the results when approached in this way and that attempts to define the precise or even general nature of any effect from these data are unlikely to be fruitful.

An additional difficulty has arisen with the advent of computer-administered tests which have largely replaced traditional paper and pencil tests in many more recent studies. A number of tests have been adapted for computer administration and, while retaining the same name, are in many respects different tests from the original. Thus the comparison of data obtained using original and automated forms is usually inappropriate.

The introduction of computer-based testing has also tended to highlight the difficulties associated with the standardisation of test administration. This relates not only to the nature of the interaction between the tester and the subject but also to the testing conditions, (noise, temperature, time of day etc), all of which have been shown to affect performance. Few studies report the nature of testing conditions and, in the case of non-automated tests, none report data on inter and intra tester reliability.

A final problem relates to the size of the effect which may be observed using a particular test. The majority of studies present results in terms of the number of statistically significant differences between the scores of the exposed group and the controls, or alternatively the statistical significance of the regression coefficient in an analysis of the relationship between a measure of exposure and test scores. However it is difficult to determine how far statistical

significance equates to biological significance. Particularly where normative test values are limited or absent.

Typically only very small differences in scores are observed (for example measured in milliseconds of reaction time) and it is accepted that a large number of factors, both individual and situational and both transitory and longer-term, can affect test performance, independently of the effect of neurotoxicant exposure. Control of all these factors within a single study is difficult to achieve. It has sometimes been noted that, despite statistical significance, the mean scores of both groups may still fall within the "normal" range of functioning for the wider population. This remains a controversial point since it has also been argued that a small shift in the distribution of scores for the group as a whole may represent important adverse consequences for some individuals within that group. Overall however the biological significance of small differences in scores remains unclear.

Given the difficulties in interpreting the neurobehavioural test data in this field the information which can be gained from these studies in relation to the objectives of the current review is rather limited. The approach adopted therefore is based on an evaluation of the quality and weight of evidence for a neurotoxic effect of solvent exposure, but does not include an assessment of the nature or size of that effect.

Quality and weight of evidence

A systematic evaluation of the quality of studies was carried out using criteria derived from the EU Guidelines for the Qualitative Evaluation of Neurobehavioural Studies (European Commission, 1997). These are shown in Table 2.

Table 2
Study Classification Criteria

1. Population of adequate size relative to the number of tests used.
2. Adoption of a subject selection method which avoids bias for the exposed group
3. Where applicable adoption of a subject selection method which avoids bias for the control group
4. Pre-stated exclusion/inclusion criteria for study participants
5. High response rate for the exposed group. Usually >60%
6. Where applicable high response rate for the control group. Usually >60%
7. Control or adjustment for important confounders/modifiers of performance, notably age, gender, social class or job type, educational level or initial intelligence and alcohol consumption
8. Inclusion of quantitative or semi-quantitative assessment of long-term exposure
9. Control for recent exposure
10. An indication of the standardisation of testing conditions

Because of the continuing controversy regarding test outcome measures, as discussed above, test selection was not included in these criteria.

Studies were identified as better studies if they fulfilled seven or more of the 10 criteria (five out of eight for studies which did not include a control group). On this basis 33 of the 58 studies were considered to be of good quality in terms of study methodology. These are marked with an asterisk on Tables I and II and are discussed below.

Nine of these 33 studies were designed to investigate exposure-effect relationships in a single group of solvent exposed workers, (i.e. they did not include a control group). Of these, six identified a significant association between a cumulative index of exposure and performance

on at least one test. One study (Rasmussen *et al*, 1985) reported the results in terms of a significantly increased risk of developing "psycho-organic syndrome" as defined by test results.

The workers studied in these six positive investigations were construction painters (3 studies), paint makers, degreasers and car body repairers. With the exception of the car body repairers and degreasers who had mean exposure durations of less than 10 years, the mean duration was more than 15 years. Of the three studies which found no effects of solvent exposure one was a study of microelectronics workers which used current exposure levels as the measure of exposure. The others were both studies of paint makers with a mean duration of exposure of less than 15 years. Both these studies used a cumulative exposure index which took into account both duration and level of exposure. Exposure in paint making factories tends to be better controlled than in end-product use and it is possible that levels of exposure were lower in these two studies.

Twenty-four of the 33 better quality studies were designed to compare the test performance of exposed and control groups and 20 of these also carried out an analysis of exposure-effect relationships. The four studies which did not do so all reported statistically significant differences between the performance of exposed and control subjects on at least one test. Three of these studies included painters and paint sprayers in their study populations. The fourth study was that which investigated identical twin pairs (occupationally exposed and non-exposed to solvents).

Of those (two-group) studies investigating exposure-effect relationships six found no relationship. Three of these used current exposure levels as an index of exposure, one used

duration in years, one a cumulative index and one both duration and a cumulative index. There would appear to be nothing in common in these populations in terms of their occupations, durations or levels of exposure to account for negative findings. The populations included painters and paint sprayers (3 studies), paint makers, videotape manufacturers and carpet layers. Exposure duration ranged from less than 10 to more than 30 years. Two of the three studies carried out in the UK fall into this group. One was an early study of dockyard painters Cherry *et al* (1985) and one a study of paint makers (Spurgeon *et al*, 1994). In the latter study it was noted that exposure levels had not exceeded current occupational exposure standards throughout the working lives of the study population. It was argued that this provided some support for the view that current standards may offer protection to workers from chronic as well as acute effects.

Of the 14 (two-group) studies which demonstrated exposure effect relationships eight used a cumulative index of exposure, four duration and one use both cumulative and duration, finding an association with cumulative but not with duration. In twelve of these studies the study population included painters, paint sprayers, varnishers or paint makers. One involved adhesive makers and one shoemakers. Not all of these studies reported exposure duration but in those that did so, this was very variable, ranging from less than five to more than 30 years. It is thus extremely difficult to discern any pattern in these results. Further, the data are not presented in a form which allows an assessment of a "no-effect" level of exposure.

As noted earlier only one useful longitudinal study has been carried out in this field. This consisted of an 18 year follow-up of a group of floor-layers originally investigated in a cross-sectional study published in 1986 (Ekberg *et* al, 1986). In the original study two groups of 25 floor-layers with a mean duration of exposure of 27 years (group 1) and nine years (group 2)

were compared with matched controls. Both groups were found to perform more poorly than controls in only one of 10 neurobehavioural tests. The follow-up study involved 41 of the original floor-layers and 40 of the original controls. All completed the same 10 tests as in the original study. For the group as a whole there was no evidence that the floor-layers had deteriorated more than the controls, that is, more than one might expect as a result of normal ageing. However, in the oldest group of floor-layers (≥ 55 years) there was evidence of a significant decline in performance on five tests in those who had experienced the heaviest exposure, in this case to solvent-based glues. The author notes that this may represent the results of very high exposures experienced 30 years previously. Thus in highly exposed people the negative effects of exposure may interact with the normal ageing process. In addition the effects on performance identified in this study appeared to be relatively large suggesting impairment equivalent to approximately five to ten years of ageing. This study involved a fairly small group of subjects and the authors note that there was considerable variation in their performance. However, the study provides the only evidence of long-term effects of solvent exposure based on data which are not derived from a cross-sectional study.

Summary

A large number of neurobehavioural studies of the effects of solvent exposure have been carried out since the mid 1970s. The majority of these are cross-sectional studies although many also carry out analyses of exposure-effect relationships using either duration or a cumulative index as a measure of exposure. Overall the results are inconsistent and inconclusive. Taking only those (33) studies judged to be of good methodological quality 26 studies found significant results either in terms of a statistically significant difference between the scores of an exposed group and control group on at least one test, or in terms of an exposure-effect relationship. A straightforward evaluation in terms of the weight of the

evidence therefore leads to a conclusion that long-term exposure to solvent mixtures can impair neurobehavioural performance.

It should be noted however, that neurobehavioural studies tend to be unfocussed in terms of the specific condition under investigation, using a wide range of tests which assess many different aspects of cognitive functioning. Thus the inconsistency in results relating to particular tests, and the lack of any discernible pattern in the test results of solvent exposed workers considerably detracts from the cogency of the evidence. This is particularly the case since differences between groups tend to be small and test performance is known to be affected by a large number of subject-based and situationally-based variables. Added to this many studies use a large number of tests and fail to carry out correction for multiple comparisons.

Despite the large body of literature in this field therefore the evidence remains equivocal. Further it is not possible to speculate on the nature or the size of any effects, other than in the most general terms, nor is it possible to determine the duration or level of exposure associated with any such effect. In terms of occupations which may be at risk the majority of study populations included painters and paint sprayers, but several other occupational groups were also represented and many studies included a number of different groups. Only one longitudinal study has been carried out. This identified an interaction between long-term heavy exposure to solvent-based adhesives and normal ageing, such that ageing effects were increased by between five and ten years in those over the age of sixty who had experienced such exposure. The author notes the small numbers involved and the wide variation in performance, particularly in the group showing the most severe effects. However this study

appears to provide the most persuasive evidence in terms of identifying an increased risk of effects which mimic accelerated cognitive ageing, in those with heavy long-term exposure.

Section IV

Studies using Symptom Questionnaires (Refer to Tables I, III and IV)

Study Characteristics

A total of 55 studies report results relating to some aspect of mood or mental health in active workers. Of these, 16 studies are concerned exclusively with mental health outcomes while the remaining 39 report these outcomes alongside neurobehavioural test results. Interest in effects on mental health appears to be increasing in the sense that 40 of these studies have been carried out since 1990 and six, concerned exclusively with psychiatric symptomatology, have been reported during the last two years.

Outcome Measures

Many studies use non-standardised symptom questionnaires with no indication of their validity or reliability or the basis for their comparison with data from other studies. However the majority of studies use at least one of the following published questionnaires:

Orëbro Questionnaire (Q16) (used in 17 studies) (Hogstedt *et al*, 1984)

A 16 item self-administered questionnaire (response Yes/No) developed specifically to screen for the effects of neurotoxicant exposure. Asks about symptoms "during the last few weeks".

Present State Evaluation (PSE) (used in 7 studies) (Wing *et al*, 1974)

A structured interview containing 140 questions designed to assess 38 psychiatric syndromes.

Profile of Mood States (POMS) (used in 7 studies) (McNair *et al*, 1992)

A mood rating scale designed to assess five mood dimensions (anxiety, depression, vigour, anger-hostility, irritability) "during the last few weeks". Self-administered.

Mood (NES) (used in 8 studies)

A version of the POMS incorporated into the computer-administered NES test battery. Very similar to the original and therefore broadly comparable. Self-administered.

(NES = Neurobehavioural Evaluation System: Baker *et al*, 1985)

Mood (NCTB) (used in 2 studies)

A version of the POMS incorporated into the manually-administered NCTB test battery. Very similar to the original and therefore broadly comparable. Self-administered.

(NCTB = National Core Test Battery: Johnson *et al*, 1987)

Minnesota Multiphasic Personality Inventory (MMPI) (used in 2 studies) (Hathaway and McKinley, 1940)

Assessment of psychiatric state and aspects of personality. 10 scales (dimensions) Self-administered.

Neurotoxic Symptom Scale (NTSS) (used in 2 studies) (WHO, 1985)

Adaptation and (German) translation of an earlier questionnaire, the Copenhagen Symptom Scale developed to assess symptoms of neurotoxicity. Self-administered. Similar timescale to Q16.

Neuropsychological Impairment Scale (NIS) (used in 1 study) (O'Donnell *et al*, 1993)

95 item checklist assessing current mood and aspects of cognitive impairment. Self-administered.

Comprehensive Psychopathological Rating Scale (CPRS) (used in 1 study) (Asberg *et al*, 1978)

37 item rating scale measuring frequency, severity and duration of psychiatric symptoms. Self-administered.

Beck Depression Inventory (BDI) (used in 1 study) (Beck *et al*, 1987)

25 items assessing previous and current symptoms of depression. Self-administered.

Zung Depression Inventory (ZDI) (used in 2 studies) (Zung, 1965)

20 item rating scale assesses frequency of symptoms of depression in the previous 4 weeks. Self-administered.

Eysenck Personality Inventory-Neuroticism Scale (EPI) (used in 1 study) (Eysenck and Eysenck, 1991)

12 statements (agree/disagree) assessing personality trait of neuroticism. No time scale. Self-administered.

Symptoms Checklist – 90 (SCL-90) (used in 1 study) (Derogatis, 1983)

90 items asking how much distress experienced by each of 90 symptoms over the past month. Self-administered.

General Health Questionnaire (GHQ) (used in 3 studies) (Goldberg, 1978)

28 items assessing severity of psychiatric symptoms (anxiety, depression, somatic symptoms, social dysfunction) "during last few weeks". Self-administered.

In addition the study by Seeber *et al* (2000) reports on the validity and reliability of two purpose-developed questionnaire (sensitivity and trait anxiety) used in their study to evaluate the contribution of psychological predisposition to symptom reporting. One very early study (Hanninen *et al*, 1976) used the Rorchach Personality Test (inkblot) which is now rarely used.

Study results

In view of the wide variety of measures used an attempt has been made to group these in terms of the particular type of effect they address, with the results presented accordingly. The symptom questionnaires used are of two basic types, those which have been purpose-developed as indicators of neurotoxicity and those which were developed in other contexts as diagnostic instruments for the assessment of mental health problems. In the former category the most frequently used symptom scale was the Q16. Of the 17 studies which included this questionnaire only five reported negative results. Of the 10 studies reporting positive findings seven reported an exposure-effect relationship.

It should be noted however that most studies show a rather low level of symptom reporting. The developers of the questionnaire (Hogstedt *et al*, 1985) suggest a cut-off score of six in terms of screening for possible neurotoxic effects. In the seven positive studies where mean numbers of symptoms in the exposed group were either reported or can be discerned from graphs, the means were uniformly well below this cut-off score. In addition the only study to

compare directly the numbers of workers in each group with symptom scores equal to or above six finds no significant difference.

Set against this, however, seven studies reported exposure-effect relationships. Of these one is in relation to a particular symptom "tingling of limbs". This study was carried out in a shoe manufacturing company where the solvent mixture included n-hexane, raising suspicions of early peripheral neuropathy in these workers, since this is a well-established specific effect of this compound. Of the remaining six studies three reported a significant relationship between symptom scores and an index of exposure which included both duration and level of exposure. The other three studies reported an increased risk of a high symptom score, adjusted for age and other potential confounders with increasing duration of exposure. In particular Chen (1999a) finds a relative risk for high symptom reporting (≥12 symptoms) in UK dockyard painters of 2.42 for up to nine years of exposure rising to 2.89 for up to 14 years and 3.41 for 15-41 years. In this study the Q16 was supplemented by six additional questions considered relevant by the authors.

Use of the Q16 has been questioned on several counts. First the questions are relatively transparent, particularly to those familiar with the conventionally accepted symptoms of solvent exposure. Moreover the questionnaire contains a number of symptoms which would come under the general heading of "non-specific" in other contexts. In recent years there has been a growing interest in the psychological determinants of symptom reporting and a concern that such factors may act as modifiers of the response to hazard exposure (Spurgeon *et* al, 1996). In this respect the study of paintmakers by Seeber *et* al (2000) which demonstrated that trait anxiety explained more of the variance in symptom reporting than did cumulative solvent exposure is of interest. It is also difficult to discriminate between acute

and chronic effects when recording symptoms in active workers. Two studies divide the Q16 symptoms into two sections, chronic and acute, and carry out their analysis accordingly. However, it is difficult to discern the basis for this either physiologically or psychometrically. In addition, the practice of conducting separate analysis on individual symptoms is questionable since the establishment of validity and reliability appears to have been carried out on the questionnaire as a whole rather than on separate items.

In relation to the psychometric properties of the questionnaire, the test re-test reliability has been shown to be high (Hogstedt *et al*, 1985). However, demonstrations of validity are difficult to find in the published literature. Pauling *et al* (1996) report one such study in which the results of the Q16 were compared with those of independent neuropsychological examination. The subjects were 40 spray painters (employment duration ≥10 years), 20 of whom had high (≥6) Q16 scores and 20 of whom had low (<6) Q16 scores. A further group of 10 workers unexposed to solvents with low Q16 scores acted as controls. The subjects were randomly selected from factory workers who routinely completed Q16 questionnaires as part of health surveillance. None had ever complained of, or been assessed for suspected organic solvent syndrome. The three groups were matched in terms of age, socio-economic status, estimated intelligence and educational level. Independent neuropsychological assessment consisting of cognitive testing and clinical interview was carried out by psychologists blind to Q16 scores. Results of cognitive testing showed that in the high Q16 group seven showed clear neuropsychological deficits and four some indications of deficits. The remaining nine subjects showed no significant cognitive dysfunction. In the low Q16 group one worker showed clear evidence of neuropsychological impairment, eight showed evidence of some impairment and 11 showed no evidence of impairment. Of the 10 unexposed workers eight showed no evidence of cognitive dysfunction and two showed some

evidence. Although the numbers in this study are small, the number of false positives and false negatives produced by the Q16 when compared with an independent measure do not provide convincing evidence of its high sensitivity or specificity as a screening tool. The results relating to the clinical interviews were slightly more encouraging in that there was generally good correspondence between the symptoms reported on the Q16 and those reported with more in-depth exploration at interview. Seventeen of the workers with low Q16 scores and all ten workers in the control group were regarded at interview as free from symptoms commonly associated with organic solvent syndrome. Eight workers were categorised at interview as showing symptoms of organic solvent syndrome and all would have been effectively identified by the Q16. However, again, the screening process when set against this criterion would have produced a number of false positives.

Given these results and the general scarcity of data on this subject it seems reasonable to be cautious about the validity of the Q16 as a measure of neurotoxicity. This said, however, the evidence relating to exposure-effect relationships in the studies described is reasonably consistent.

Two further neurotoxicity questionnaires used in relation to solvent exposure are the Neurotoxicity Symptom Scale (NTSS) used in two German studies and the Neuropsychological Impairment Scale (NIS) used in one study in the USA. In all three studies significant associations were found between symptom reporting and a cumulative index of exposure.

Other studies have used a range of non-standardised symptom questionnaires. Because of the different formats of these and the range of symptoms included it is difficult to summarise the

data. However, 16 studies using this kind of questionnaire reported a significantly higher frequency of symptom reporting in the exposed group and one reported an exposure-effect relationship. Three studies reported no significant findings.

A number of studies have used well-established mental health diagnostic tools in preference to the newly developed questionnaires which purport to measure neurotoxicity. The most commonly employed is the Profile of Mood States (POMS). This is self-administered, either in its original paper and pencil form (7 studies), as part of the non-computer administered National Core Test Battery (NCTB) (2 studies) or as part of the computer-administered Neurobehavioural Evaluation System (NES) (8 studies). The POMS is intended to measure transitory mood states rather than more enduring psychiatric conditions and in the context of these studies would appear to represent an assessment of mood lability. The results of studies using this measure do not find strong evidence of an association with solvent exposure. Eleven studies reported negative results and the results of one other were very poorly reported with an absence of statistical analysis. Of the five studies reporting effects, three reported a significant difference between exposed and control groups which occurred in all five mood scales but no exposure-effect relationship. Two studies reported an association with exposure, one in terms of duration and the other using a cumulative exposure index involving both duration and level. One further study assessed mood using a visual analogue scale as an alternative to the POMS. In this study a significant increase in acute but not chronic mood disturbance was reported in the exposed group. On balance therefore although there is some evidence for an association between solvent exposure and mood lability this is not strong.

Other studies have employed more detailed forms of psychiatric assessment such as structured interviews, notably the Present State Evaluation (PSE) and more extensive questionnaire measures, notably the Minnesota Multiphasic Personality Inventory (MMPI), the 90-item Symptoms Checklist (SCL-90) and the Comprehensive Psychopathological Rating Scale (CPRS). These instruments are intended to identify specific diagnostic categories. Six of the seven studies which employed the PSE reported no significant findings. The remaining study found no significant excess of receiving any diagnosis (schizophrenia, affective psychosis or neurotic disorders) in exposed subjects (painters). However, within the group which received a diagnosis, scores for specific and non-specific neurotic symptoms were higher in painters than in controls and higher in painters with greater cumulative exposure scores than with lesser scores. A study carried out amongst dockyard painters in the UK and in China using the Eysenck Personality Inventory also identified a higher risk of neuroticism in exposed workers, which was significantly associated with duration of exposure. In the UK sample the odds ratio was 2.38 for 5-9 years duration, rising to 7.05 for 10-14 years. However, for 15-41 years duration this dropped to 1.76.

Significant findings were also reported in the studies using the SCL-90, the MMPI and the CPRS. In the case of the SCL-90 no details are reported other than an increased frequency of symptoms in the exposed group. Similarly the study employing the CPRS reported results simply in terms of increased symptomatology in the exposed group, although this was noted to be particularly in relation to "neurasthenic" symptoms. In the case of the MMPI it was noted that five of the 30 controls and 15 of the 22 exposed subjects had abnormal psychological profiles. In the exposed group these were characterised by anxiety, depression, somatoform and psychotic disturbances.

Three studies report the use of specific measures of depression (Beck Depression Index, Zung Depression Inventory). Neither of the two studies using the Zung scale reported any significant findings. In the third study exposed subjects (painters) had significantly higher mean scores on the Beck Index but only three painters out of a population of 89 reached borderline scores for clinical depression. This particular study involved retired workers in receipt of a normal (non-disability) pension. Finally three studies used the General Health Questionnaire (GHQ) which contains separate scales for anxiety, depression, somatic symptoms and social dysfunction. None reported significant findings.

Exposure

All the study populations reported here were exposed to solvent mixtures and in 38 studies the exposed group comprised or included painters or paint makers. Most studies report the duration of solvent exposure (mean and range) in their exposed population. These data are frequently used in the analysis of exposure-effect relationships either alone or in combination with various other measures of exposure levels (e.g. historical monitoring data, job type, hygienist estimates etc) to form a cumulative exposure index. These analyses are important in terms of establishing an effect since the demonstration of an exposure-effect relationship provides much stronger evidence than does the simple demonstration of a significant difference between two groups in cross-sectional studies. However few of these data are in a form which can assist in determining the degree of risk following a particular duration and/or level of exposure. In this dataset, relating to psychiatric symptomatology and symptoms of neurotoxicity, the most important studies are those of Chen *et al* (1999a, 1999b) concerned with dockyard painters, particularly that carried out in the UK in a population of active workers. After adjustment for confounders this study identified, for painters with a score of ≥12 symptoms, a relative risk of 2.27 in those with 1-4 years of exposure, 2.42 with 5-9

years, 2.89 with 10-14 years, and 3.41 with more than 15 years exposure. Analysis of the effect of time since stopping painting in this group also showed relative risks of 2.76 for active painters, 3.02 for those within 1-10 years of stopping, 2.50 for those who had not worked for 11-18 years and 2.66 for those who had not worked for >19 years.

Summary

Among 55 studies concerned with symptoms of neurotoxicity and/or psychiatric disturbance approximately twice as many report positive findings as report negative findings. About one quarter of the studies report exposure-effect relationships. There is wide variation in the measures used to assess neurotoxicity or psychiatric disturbance and not all have demonstrable validity and reliability. In general there appear to be fewer positive findings when established psychiatric measures of mood disturbance, anxiety, depression and other mental health problems are employed. Most positive findings relate to measures developed specifically for the assessment of neurotoxicity. The data relating to the Q16 are the most persuasive particularly where exposure-effect relationships have been demonstrated, (7 studies) although there is some doubt about the validity of the Q16 as a diagnostic or screening tool. The most important study in terms of establishing an association between symptom reporting and exposure duration appears to the that of Chen *et al* (1999a) which uses the Q16 + 6 symptoms and provides more specific information about the risk associated with increasing years of exposure.

Section V

Cohort and Case-referent Studies (Refer to Tables V, VI and VII)

Results of investigations discussed in the previous sections indicated that cross-sectional studies comparing two groups of workers (solvent exposed and non-solvent exposed) on a range of neurobehavioural or self-report measures provide some supportive evidence for an effect on the nervous system, but do not provide information about the particular nature of that effect. The difficulties surrounding this conclusion become apparent when other sources of evidence in this field are considered. In occupational health in general, attempts to determine whether exposure to a certain substance (or in this case a mixture of substances) increases the risk of developing a certain condition have traditionally employed either cohort studies (retrospective or prospective) or case-referent (case control) studies. Inspection of the literature on solvent exposure identified three cohort studies (published in 1980, 1989 and 1992) and 16 case-referent studies published between 1976 and 1995. A particular source of difficulty in this field however is the problem of case definition which is a pre-requirement of both types of study. Before discussing the results of these 19 epidemiological investigations therefore a discussion of the issues surrounding case definition and diagnosis is included below.

Approaches to case definition

It was noted in section I that evidence in this field tends to be largely in terms of the observation of functional rather than structural or biochemical changes. This is not unusual in conditions involving degeneration of the nervous system or psychiatric disorders. However, such conditions and disorders tend to be classified in terms of certain patterns of symptoms or changes in functioning. In relation to the neurotoxic effects of solvent exposure

attention has focussed both on impairment of cognitive functioning and on symptoms of psychiatric disorder. In each case attempts have been made to identify a particular pattern of changes which might be regarded as typical of solvent-related effects. The evidence employed is derived first from neurobehavioural studies and studies of symptom reporting and secondly from case series. The inconsistencies in the results of neurobehavioural and symptom-based studies have already been discussed. In addition to these studies, however, a number of publications can be found in the literature which appear to come under a broad heading of case series reports. These are discussed below.

Case series

In total 18 such reports were identified. Eight of these report the neuropsychological test results and/or psychiatric condition of a patient group only. Ten others appear to be presented as prevalence studies in that they report the results of a comparison between a solvent-exposed group and a referent group. However, since in each case members of the solvent-exposed group were already diagnosed as having a solvent-related condition, or were in the process of disability or litigation assessment in relation to solvent exposure, they appear to share the characteristics of case series rather than epidemiological studies. All 18 reports are concerned with patients referred or self-referred to Occupational Medicine Clinics. Twelve emanate from the United States, (seven from one clinic[1], three from a second clinic and two from a third clinic), and include patients either involved in or having completed litigation. The remaining reports come from Scandinavian countries (three from Norway, two from Finland and one from Denmark). Although it is not explicitly stated, the presence of the patients at Occupational Medicine Clinics in these reports suggests that they are involved in assessment for possible disability pensions.

Most of the examinations carried out include a full neuropsychological assessment using the Wechsler Adult Intelligence Scale, the Wechsler Memory Scale and/or the Halstead-Reitan Neuropsychological Battery. These test batteries are extremely lengthy and provide a detailed assessment which goes beyond that provided by the relatively short tests commonly employed in epidemiological studies. They also involve the use of qualitative as well as quantitative information. In addition to neuropsychological tests there is frequent use of scales which measure psychiatric conditions and occasional use of structured clinical interviews.

Since the patient groups are pre-selected on the basis of diagnosed or suspected problems the fact that all 18 investigations report significant cognitive impairment and/or psychiatric disturbance in these groups is unsurprising. Their potential value however, lies in the possibility of identifying consistent patterns of impairment and symptom reporting which might be hypothesised to be typical of solvent-related effects. From the point of view of assisting with the identification of these patterns however, these data are problematical. Although the test batteries employed are standardised in terms of providing normative values and thus intended for diagnostic purposes, the investigators tend to use a variety of sub-tests, presumably on the basis of clinical preference, rather than administering the whole battery. Thus the results are dependent on the particular sub-tests included. In addition results are frequently presented in terms of a broad diagnosis rather than in terms of actual scores, for example “clinically elevated scores” or “impairment of psychomotor function”. Overall, in so far as can be discerned from the data, there would not appear to be any consistent pattern in the results beyond a general indication of cognitive impairment and psychiatric disturbance

[1] It is not clear from the numerous reports emanating from the Pittsburgh Occupational Medicine Clinic whether

in these patients. As with all case series, however, the selective nature of the group would in any case limit the generalisability of the results and could only point to possible areas for further scientific study.

Consensus-based case definition and diagnostic criteria

As a result of controversy and concern relating to questions of definition and diagnosis two international meetings have been convened in an attempt to reach a consensus on this matter. The first of these was held in Copenhagen in 1985 under the auspices of the World Health Organisation (WHO 1985). As a result of this meeting a classification system and a set of diagnostic criteria for "Solvent-induced Chronic Toxic Encephalopathy" (CTE) was proposed. These are shown in Table 3.

Table 3
Classification of Chronic Organic Mental Disorders, (WHO 1985)

Disorder	Pathophysiology	Course	Clinical manifestations	Reduced CNS function
Organic affective syndrome (type I)	Unclear	Days to weeks No sequelae	Depression, irritability, loss of interest in daily activities	-
Mild chronic toxic encephalopathy (type II)	Unclear	Insidious onset Duration: weeks to months, reversibility questionable	Fatigue, mood disturbance, memory complaints, attentional complaints	Psychomotor function (speed, attention, dexterity); short-term memory; other abnormalities common
Severe chronic toxic encephalopathy (type III)	Unclear, often associated with structural CNS damage	Insidious onset Duration: indefinite, usually irreversible	Loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning; memory impairment; impairment of abstract thinking; impaired judgement; other disturbances of cortical function; personality change	Types of abnormality similar to mild toxic encephalopathy; more pronounced and pervasive functional deficits; some neurophysiological and neuroradiological test abnormalities

these represent separate groups of patients or updates on an accumulating group.

Later in the same year a further meeting of researchers and occupational medicine experts was convened in Raleigh in the United States to address similar questions (Anonymous, 1985). They produced the classification system shown in Table 4.

Table 4
Effects of solvents on the central nervous system: proposed categorization by type: Working Group, Raleigh, USA (1985)

Category	Effects
Type 1: Symptoms only	
Symptoms	Non-specific symptoms, such as fatigue, memory impairment, difficulty in concentration, and loss of initiative
Course	Reversible if exposure is discontinued
Cognitive deficits	No objective evidence of neuropsychiatric dysfunction
Type 2A: Sustained personality or mood change	
Symptoms	Marked and sustained change in personality involving fatigue, emotional lability, impulse control, and general mood and motivation
Type 2B: Impairment of intellectual function	
Symptoms	Difficulty in concentration, impairment of memory, and a decrease in learning capacity
Cognitive deficits	The symptoms are accompanied by objective evidence of impairment
Neurological deficits	There may be minor neurological signs
Residua	The complete reversibility of Type 2B is questionable
Type 3: Dementia	
Symptoms	Marked global deterioration in intellect and memory
Neurological deficits	Often accompanied by neurological signs or neuroradiological findings
Residua	Poorly reversible at best, but generally non-progressive once exposure has ceased

Van der Hoek *et al* (2000) have compared and contrasted the two systems and examined their use in subsequent research and case reports. Having identified 30 articles which involved the diagnosis of CTE between 1985 and 1998, they observed considerable variation in the reporting of solvent exposure, in the tests used, and the extent to which potentially confounding conditions were excluded. In particular they noted that only six articles used both the WHO diagnostic criteria and the WHO or Raleigh classification system. In a subsequent review (van der Hoek *et al*, 2001) these authors investigated by questionnaire the routine diagnostic procedures used in different countries for CTE induced by solvents. Although most of those who responded (18 experts working in 18 diagnostic centres) agreed

that procedures should involve interview, neurological, physical and neuropsychological examinations, the tests used varied widely as did the criteria for CTE. They noted that the percentage of patients receiving a positive diagnosis varied from 6% - 70% across different clinics. These variations are supported by the results of a survey by Triebig and Hallermann (2001) who recorded the number of cases of CTE diagnosed in different countries across the European Union between 1980 and 1998. Data were obtained by questionnaire from medical and government health officials in the countries concerned. For those (seven) countries returning data the total number of cases for the period varied between approximately 5,500 in Denmark to seven in Switzerland. For all these countries except Belgium (total 60 cases) there has been a reduction in the number of cases in recent years.

To place these figures in the context of the size of the workforce in each country the authors calculated an incidence rate per million employed for the years 1994 and 1997, shown below.

Incidence (new cases) of CTE/million employed

	1994	**1997**
Denmark	45.3	16.8
Finland	6.9	8.5
Germany	0.6	0.5
Italy	0.4	0.1
Norway	47.7	-
Sweden	43.0	13.0
Switzerland	-	0.3

- = no data or not calculable

(from Triebig and Hallermann, 2001)

The authors point to differences in diagnostic criteria and assessment methods, differences in criteria for causality (in terms of levels and durations of exposure required) and differences in legislation to account for this variation.

While most European countries now include CTE in their list of recognised occupational diseases the procedures by which such cases are recognised, and acknowledged appears to be heavily dependent on the nature of the legal system in the respective country.

The results of these surveys indicate at least two concerns relating to the definition and diagnosis of CTE. First, although an attempt has been made to reach a consensus about the condition, the consensus position appears to be either ignored or at least interpreted very differently in different countries and in different clinics within countries. Secondly, although consensus statements exist on the conditions, the methods of assessment are expressed only in the broadest terms, leading to wide variation in test methods and in the interpretation of results. It should also be noted that in the list of case series presented in Table V six different names for the condition are used. Two authors from the same country (Norway) both writing after 1985 also use different names. Only two authors uses a label derived from one of the classification systems, (Raleigh 2A/2B).

Follow-up studies of diagnosed patients

Publications which report follow-up and re-assessment of individuals diagnosed with CTE provide some indication of the stability of the diagnosis, although not its consistency between clinics. Nine such reports were identified following patients between 6 months and 13 years post diagnosis. Interestingly all these reports label the condition CTE, although only half refer to one of the classification systems. The results of re-assessment tend to confirm the original results in virtually all cases, although a few subjects showed some improvement in test scores. Only 20 subjects (out of a total of approximately 150 studied in all the reports) were reported to have deteriorated. Most authors regard this finding as providing evidence that CTE is not a progressive condition if the patient is removed from exposure. One report

however questioned the initial diagnosis of CTE (Gade *et* al 1988). In this investigation 20 cases of CTE diagnosed two years previously, were matched with 20 referents recruited from the hospital's Department of Orthopaedic Surgery (mainly limb fractures). Administration of psychological tests showed that the test results of the CTE patients were unchanged from those recorded earlier. However, following adjustment for age, educational level and initial intelligence it was also shown that they did not differ significantly from those of the referents.

In general, given the uncertainties surrounding the definition of the condition, the diagnostic criteria and the assessment methods, the results of follow-up studies provide little additional information in this field. These uncertainties also tend to affect the interpretation of cohort and case-control studies which are discussed below. In the absence of a more specific definition of the condition associated with solvent exposure these studies have focussed either on "psychiatric disorders" or on "dementia" as the outcome of interest.

Cohort studies

Three cohort studies were identified including the influential study by Mikkelsen conducted in 1980. This reported on a cohort of 2,601 painters and 1,790 bricklayers followed between 1971 and 1975. No increased risk of psychiatric disorders in general was identified in the painters but there was a significant increased risk of "dementia", (OR = 2.0) after dementia associated with specific causes (alcoholism, head trauma or cardiovascular disease) had been excluded. Whether or not the risk of "dementia" in painters was already highly suspected at that time in Denmark leading to increased diagnosis by physicians has always been a controversial point. In addition it has been established that "dementia" as defined in the context of this study was a much less severe condition than "dementia" as defined in the UK. Mikkelsen's study also identified a significantly increased risk of alcoholism in painters when

compared with a cohort drawn from all Copenhagen blue-collar workers over 30 years old, although compared with bricklayers the risk for painters while increased was non-significant.

A study by Gubéran *et al* (1989) using a cohort defined by the 1970 Geneva census (1,916 painters and 1,948 electricians) also found no increased risk of general psychiatric disability in painters, excluding alcohol-related disorders. When such disorders were included the RR was 10.9. Further, painters were shown to have an increased risk of mortality due to alcoholism (SMR 625) and cirrhosis (SMR 159). There was also a slightly increased risk specifically of somatic conditions in painters (RR 1.6).

The third cohort study, carried out by Lundberg *et al* (1992) also identified an excess risk of alcoholism in painters. Comparing them with a cohort of carpenters, painters were found to have a significant excess risk of early retirement (RR 8.0) and a significant excess risk of psychiatric care (RR 1.5) both of which were mainly associated with alcoholism.

The findings of these three studies appears to point to an increased risk of mental health problems in painters which may be related to alcohol. The possibility that painters are more vulnerable to disability as a result of an interaction between solvent exposure and alcohol has been suggested but remains controversial.

Case-referent studies

A total of eight case-referent studies based on awards of disability pensions for psychiatric disorders have been carried out. Most studies carry out an analysis for total psychiatric disorders and for specific conditions separately. In the case of the latter, particular difficulties associated with the comparability of diagnostic labels arise. Equally this applies

to the determination of solvent exposure which in some cases is based on job title and in others on questionnaire data or interview derived either from the patient or a proxy informant.

Only one study finds a significantly increased risk (RR 2.0) for disability pension due to "dementia" associated with solvent exposure. This study was also carried in Denmark in 1980 (Olson and Sabroe, 1980) and the questions raised about Mikkelsen's study may similarly apply. Three studies find an increased risk of disability pension for all psychiatric disorders but not for specific conditions separately. Riise and Moen (1990) found an increased risk for mates working on oil tankers (as opposed to dry cargo ships) (OR 5.11). Brackbill *et al* (1990) noted an increased risk for all painters (OR 1.42) and construction painters (OR 1.47) but not for spray painters. The increased personal protection habitually worn by spray painters was suggested as an explanation for this finding. Axelson *et* al (1976) also found an increased risk (RR 1.8) of disability pension due to non-specific psychiatric disorders (excluding alcoholism) in occupations involving solvent exposure (painters, varnishers and carpet layers).

The study by Olson and Sabroe (1980) noted earlier, in addition to the findings relating to dementia, also found an increased risk with solvent exposure for disability due to psychiatric diagnosis in general (RR 2.8) as well as for neurosis specifically (RR 3.11). Two further studies identified an association specifically with neurotic disorders but not with psychiatric conditions in general. Van Vliet *et al* (1990) reported an OR of 2.3 when a history of solvent exposure was derived from questionnaires and Lindstrom *et al* (1984) reported an OR of 5.5 using job title (painter) as the indicator of exposure.

Two studies report negative findings. Nelson *et al* (1994) found an inverse relationship between solvent exposure and disability retirement for neurological disease in car factory workers. Van Vliet *et al* (1987) noted that in a comparison of painters and other construction workers who had all received disability pensions for neuropsychiatric disorders, there was no indication of a "typical symptom complex associated with CTE" in the painters.

Overall these results appear to show some consistency in terms of demonstrating an increased risk of psychiatric disorders in solvent exposed workers. All the studies were carried out before 1995 and therefore would presumably have included individuals who experienced the higher levels of occupational exposure prevalent in the 1970s and 1980s. The differences in the results between studies can presumably be explained to some extent by inconsistencies in diagnostic labelling, and by variations in the reliability of both the medical and exposure information. Questions remain about the validity of accepting "psychiatric disorders" as the diagnostic category of interest, given the wide spectrum of disorders encompassed by this term. In this respect the findings of van Vliet *et al* (1987) which question the relevance of this category to CTE are of note.

Two studies, (Labrèche *et* al, 1992 and Cherry *et* al, 1992) have investigated the association between solvent exposure and admission to psychiatric care. Both used careful validated exposure assessments. No increased risk for admission to psychiatric care in general, or specifically with a diagnosis of organic dementia, psycho-organic syndrome or cerebral atrophy was found. By contrast Rasmussen *et al* (1985) found that previous solvent exposure (assessed by telephone interview or questionnaire) was more frequent in men admitted to a geriatric ward with a neuropsychiatric diagnosis than with another diagnosis. This is again a

Danish study and, given the high profile of this subject in Denmark at the time, questions can be raised about possibly reporting bias among the subjects.

Five studies have specifically addressed the question of Alzheimer's disease. Kukull *et al* (1995) found that of patients entering a health maintenance programme in the United States those with a diagnosis of Alzheimer's disease were significantly more likely to have had previous solvent exposure than those with a non-neurological disease (OR 2.3 for the group as a whole, OR 6.0 for males only). Information on solvent exposure was provided by proxy informants and again reporting bias cannot be discounted. It is not reported whether these individuals had been involved in litigation or claims for disability benefit. Of the remaining studies three were case-referent studies involving Alzheimer's patients and one, carried out in the UK (O'Flynn *et* al, 1987) was a case-referent mortality study. None of these four studies identified an increased risk of Alzheimer's disease associated with solvent exposure.

Summary

The results of case-referent and cohort studies are difficult to interpret primarily because of difficulties associated with case definition. Because of the prevailing opinion that CTE involves both cognitive impairment and psychiatric disorder epidemiological studies have focussed on these outcomes. However, at least one investigator has questioned the correspondence between definitions used in case-control and cohort studies and the condition which clinicians identify as CTE. The strongest evidence is for an association between solvent exposure and psychiatric disorder which comes from the case-referent studies involving patients with disability pensions. However, the evidence of psychiatric disorders as a whole is stronger than for any more specific diagnostic category. The results are also

open to question in terms of the assessment of solvent exposure which varies considerably between studies.

There is fairly consistent evidence from cohort studies off an increased risk of alcohol-related problems in solvent exposed workers. This has been the subject of considerable debate but the possible relationships between solvent-exposure and the effects of alcohol consumption are currently unclear.

If psychiatric disease occurs more frequently in solvent-exposed workers this does not appear to be reflected in psychiatric admissions, although this finding may be due to the nature of psychiatric admissions in the areas studied. For example such admissions may be largely the result of severe acute episodes, which may not necessarily occur in patients with long-term psychiatric disorders.

The original finding by Mikkelsen of an association between solvent exposure and "dementia" does not appear to have been replicated in non-Danish studies. This seems most likely to reflect a difference in disease classification. No studies have found a relationship with solvent exposure when dementia has been considered specifically as Alzheimer's disease.

Section VI

Executive Summary and Conclusions

The current report is intended to provide information to IIAC as a basis for their considerations on whether the effects of occupational exposure to organic solvents should be recommended for inclusion in the UK list of prescribed diseases. Taking into account the legal requirements of prescription set out in the IIAC report "Conditions due to Chemical Agents" (2002) the following specific objectives of the report were defined as follows:

(i) to determine whether the existing literature provides evidence for the development of chronic adverse effects on cognitive functioning or psychiatric disorders following long-term occupational exposure to organic solvents

(ii) to determine whether the size and nature of any identified chronic adverse effects, together with valid and reliable methods of assessment can be defined from the current literature

(iii) to determine whether the duration and level of exposure associated with any identified chronic adverse effects can be determined from the current literature

(iv) to determine whether, from the current literature, it is possible to determine the size of the risk of developing adverse effects on cognitive functioning or psychiatric disorders, associated with long-term occupational exposure to organic solvents.

Methodology

A structured, systematic literature search was undertaken according to the principles of the evidence-based review process. Seven databases were searched using pre-defined search terms and criteria. The initial search identified 206 papers of which 123 were retained following application of inclusion and exclusion criteria. 58 papers reported studies

involving neurobehavioural testing of solvent-exposed workers. Of these 39 also reported questionnaire-based data relating to symptom reporting. A further 16 papers reported studies involving symptom data alone. Eighteen papers were identified which described case series and a further nine papers reported on follow-up studies of diagnosed patients. Nineteen papers reported cohort or case-referent studies. Finally three papers discussed diagnostic criteria and case identification in the context of the wider European experience. Details of each type of study were recorded in a series of Tables and the data were evaluated in the light of the objectives of the review. Results were discussed in three sections (i) studies involving neurobehavioural testing (ii) studies involving questionnaire data on symptomatology (iii) cohort and case-referent studies. Section (iii) also contained a discussion on case definition and diagnostic criteria and included reference to case series and follow-up studies.

Results

(i) Neurobehavioural studies

A total of 58 studies were identified which involved neurobehavioural testing of active workers and one of retired (non-patient workers). The majority of these studies were cross-sectional in design, either involving a comparison of the performance of exposed workers and a control group or investigating the relationship between test performance and a measure of exposure in a single group of exposed workers. On the basis of criteria developed from EU recommendations on the evaluation of neurobehavioural studies, 33 studies were judged to be of good methodological quality. Taking these studies alone, the weight of the evidence supports the view that long-term exposure to organic solvents can result in impairment of cognitive functioning. However, the wide variation in the tests used and in the approaches to assessment of exposure do not allow any conclusions to be reached on the size or specific nature of the effect, or on the duration of exposure required to produce that effect. It is also

noted that the studies include a number of different occupational groups exposed to a variety of solvent mixtures.

Only four longitudinal studies were identified and only one of these was considered useful for the purposes of the current review. This study, (Nordling Nilson, 2002) consisted of an 18 year follow-up of a group of 50 floor-layers and 50 referents originally studied in a cross-sectional investigation in 1986. The follow-up study identified a significant effect on cognitive functioning which appeared to interact with age in that it occurred only in the sub-group over the age of 55 years. Although only small numbers of subjects were involved, the superiority of longitudinal over cross-sectional data makes this the most persuasive evidence of solvent-related effects which can be derived from the neurobehavioural data.

(ii) Symptomatology studies

A total of 55 studies were identified which reported results describing symptomatology, mainly in relation to mood or mental health. The majority used at least one questionnaire which was standardised in the sense that its original publication was accompanied by data on validity and/or reliability. The studies were exclusively cross-sectional in design. Those which used a questionnaire which was purpose-developed to assess general neurotoxicity (mainly the Q16) reported a high percentage of positive findings. Those which used measures developed in other contexts, to assess specific psychiatric disorders such as anxiety and depression, reported fewer effects. Several authors reported exposure-effect relationships. The most useful study in this respect was that carried out by Chen *et al* (1999a) in UK dockyard painters which identified a significant increased risk of a high level of symptom reporting (i.e. above the recommended Q16 threshold for screening) with

increasing duration of exposure. (RR 2.27 for <5 years exposure, rising to 3.41 for >15 years exposure).

(iii) Case-definition

Studies involving neurobehavioural testing or symptom reporting appear to have achieved only limited success in terms of defining the specific nature of the adverse effects of solvent exposure. Reports of patient investigations were considered as an alternative source of information in this respect. Eighteen such investigations were identified but none provided evidence of a consistent pattern of effects which would, for example, be identifiable from the type of information sources typically employed in cohort and case-referent studies. Follow-up studies of diagnosed cases were similarly uninformative in this respect. The results of follow-up studies were fairly consistent in demonstrating that the test results of patients remain stable following original diagnosis. This was interpreted by most authors as evidence that effects were unlikely to be progressive if patients were removed from solvent exposure. However, one author, on comparing the follow-up results of patients with those of non-patient referents, found no differences after adjustment for potential confounders, leading him to question the original diagnosis (Gade *et al*, 1988).

Two international workshops have been convened (both in 1985) in an attempt to reach a consensus on disease classification and diagnostic criteria for conditions associated with long-term solvent exposure. These meetings reached broadly similar conclusions although there were some classificatory differences. At this point most countries appeared to adopt the term Chronic Toxic Encephalopathy (CTE) to describe the condition. However recent surveys (van der Hoek *et al*, 2001; Triebig and Hallermann, 2001) carried out across EU member states have revealed a lack of application of either of the classification systems or of

the diagnostic criteria, together with wide variation in assessment methods and interpretation of results. Partly as a consequence of this there continues to be large differences between countries in terms of the number of diagnosed cases.

(iv) Cohort and case-referent studies

Cohort and case-referent studies have tended to focus on two types of case-definition, those relating to psychiatric disorders of various types and those relating to cognitive impairment, notably forms of dementia. The early influential study by Mikkelsen published in 1980 identified a significant increased risk of "dementia" in painters. However questions about the nature and severity of this condition as defined in the Danish context compared to that in some other countries, have often been raised. Four subsequent case-referent studies have failed to find any association between solvent exposure and Alzheimer's disease. However, one study in the USA did find that males diagnosed with Alzheimer's were significantly more likely to have had previous solvent exposure.

Eight case-referent studies were identified which focussed on patients in receipt of disability pensions following diagnosis of a psychiatric disorder. Six of these studies demonstrated a significantly increased risk associated with previous solvent exposure although the evidence tends to be stronger for psychiatric disorders in general than for any specific conditions. Two studies which compared younger psychiatric and non-psychiatric hospital admissions did not identify any increased exposure to solvents in psychiatric cases. However, a study of geriatric admissions found that those with a neuropsychiatric diagnosis did, on the basis of questionnaire and interview data, report more previous solvent exposure. Inevitably questions can be raised in each study about the quality of the information relating to diagnosis and/or solvent exposure, particularly in social and legislative climates where CTE

or a similar condition is readily acknowledged. Again the weight of the evidence tends to support the existence of an effect. However, the particular nature of this is difficult to define.

Conclusions

In relation to the pre-stated objectives of the current review the following conclusions are drawn:

Objective (i)

Taking simply a "weight of evidence" approach the results of studies which involve neurobehavioural testing, and symptom reporting, as well as results from cohort and case-referent studies, suggest that long-term occupational exposure to organic solvents can result in adverse effects on the central nervous system. However a number of qualifications to this conclusion should be made. These are noted in relation to objectives (ii), (iii) and (iv) below.

Objective (ii)

Although the published literature on this subject is very large it is difficult to be specific about the nature of any adverse effect beyond a general statement relating to effects on cognitive functioning and mental health.

Neurobehavioural studies are the most numerous in this field but the results of these are the least persuasive. These studies use a wide variety of tests and no consistent pattern in the results can be discerned. Most differences in performance between exposed and control groups are very small and their biological or social significance is unclear. Neurobehavioural studies in this field are essentially "broad brush" investigations which can only suggest the possibility of effects, which then require further investigation. It is not possible for studies of this type to provide any more precise information on the nature of cognitive changes which

may occur in response to solvent exposure, since this requires a much more detailed theoretically-based approach. No studies using such an approach have so far been carried out.

It should also be noted that the dataset contained only one useful longitudinal study. The results of this study suggested effects which were (a) associated with high levels of past exposure and/or (b) interacting with age to produce greater cognitive decline in older workers.

Studies which investigate reported symptomatology provide most consistent evidence of effects when questionnaires developed specifically to screen for neurotoxicity are used. Data on the sensitivity and specificity of these questionnaires (notably the Q16 which has wide application) is currently limited however. Studies which use questionnaires designed to identify particular types of psychiatric disturbance have produced less consistent results. Case-referent studies appear to have fairly consistently demonstrated an increased risk of general psychiatric disorders in those with previous solvent exposure, but less consistently an association with specific conditions. Information from case series similarly indicates rather general and inconsistent effects on cognitive functioning and mental health.

Attempts to reach international consensus on case definition and diagnostic criteria have met with limited success in the sense that recent surveys have indicated wide variation in the application and interpretation of these. Similarly there is no universal agreement on appropriate methods of assessment. Unsurprisingly therefore there are large differences in the number of diagnosed cases in different countries in the European Union.

Objective (iii)

The identification of the level or duration of solvent exposure required to produce adverse effects presents considerable difficulties. Criteria agreed at the international workshops included a requirement for at least 10 years exposure for a diagnosis of solvent-related CTE. However it is difficult to find an evidential basis for this in the literature. For example, effects appear to have been demonstrated in some workers exposed for less than five years. The influence of exposure level versus duration, and how these two aspects may interact, is currently unclear. While many studies have demonstrated exposure-effect relationships using a cumulative exposure index (level and duration) it is not possible to discern an adverse effect level from these data.

Objective (iv)

The majority of studies in this field do not present data in terms of the relative risk of developing particular effects. In this respect the only informative studies are the cohort and case-referent studies and the cross-sectional study of symptom reporting carried out by Chen *et al* (1999). The results are suggestive of an increased risk of psychiatric disorders in workers with previous solvent exposure. The results are inconsistent in terms of the size of the risk, with relative risks ranging from less than 2 to more than 5 in some studies. There are numerous methodological aspects of these studies, notably in relation to case identification and exposure classification, which may account for these inconsistencies. Further the general category of psychiatric disorders is very broad. The question of the influence of the social and legislative climate in the countries concerned on the pattern of disability awards has also been raised. There is little convincing evidence of an association between solvent exposure and an increased risk of Alzheimer's disease and the original Danish investigations (Mikkelsen, 1980; Olson, 1980) remain the only studies to identify an

association with “dementia”. The characteristics of this condition, as defined in the Danish context, are unclear but are not regarded as synonymous with Alzheimer’s disease.

References

Abjornsson G, Palsson B, Bergendorf U *et al*. Long-term follow-up of psychological distress, social functioning, and coping style in treated and untreated patients with solvent-induced CTE. Journal of Occupational and Environmental Medicine 1998;40(9):801-807

Anonymous. Proceedings of the Workshop on Neurobehavioural Effects of Solvents. October 13-16, 1985, Raleigh, North Carolina, USA. Neurotoxicology 1986 Winter;7(4):1-95

Antti-Poika M. Prognosis of symptoms in patients with diagnosed chronic organic solvent intoxication. International Archives of Occupational and Environmental Health 1982;51(1):81-89

Arlien-Soborg P, Bruhn P, Gyldensted C *et al*. Chronic painters' syndrome. Chronic toxic encephalopathy in house painters. Acta Neurologica Scaninavica 1979;60(3):149-156

Åsberg M, Montgomery D, Perris C *et al*. The Comprehensive Psychopathological Rating Scale. Acta Psychiat. Scand. 1978;Supp 271:5-29

Axelson O, Hane M, Hogstedt C. A case-referent study on neuropsychiatric disorders among workers exposed to solvents. Scandinavian Journal of Work, Environment and Health Mar 1976;2(1):14-20

Baker EL, Letz R and Fidler A. A computer-administered neurobehavioural evaluation system for occupational and environmental epidemiology. Journal of Occupational Medicine 1985;27:206-212

Baker EL, Letz RE, Eisen EA *et al*. Neurobehavioural effects of solvents in construction painters. Journal of Occupational Medicine 1988;30(2):116-123

Beck AT and Steer RA. Beck Depression Inventory manual. San Antonio, TX: Harcourt Brace, 1987

Berstad J, Flekkoy K and Pedersen ON. Encephalopathy and polyneuropathy induced by organic solvents. Journal of the Oslo City Hospitals 1989 Jun-Jul;39(6-7):81-86

Bleecker ML, Bolla KI, Agnew J *et al*. Dose-related subclinical neurobehavioural effects of chronic exposure to low levels of organic solvents. American Journal of Industrial Medicine 1991;19(6):715-728

Bolla KI, Schwartz BS, Agnew J *et al*. Subclinical neuropsychiatric effects of chronic low-level solvent exposure in US paint manufacturers. Journal of Occupational Medicine 1990;32(8):671-677

Bolla KI, Schwartz BS, Stewart W *et al*. Comparison of neurobehavioural function in workers exposed to a mixture of organic and inorganic lead and workers exposed to solvents. American Journal of Industrial Medicine 1995;27(2):231-246

Bowler RM, Lezak M, Booty A *et al*. Neuropsychological dysfunction, mood disturbance and emotional status of munitions workers. Applied Neuropsychology 2001; 8(2):74-90

Bowler RM, Mergler D, Huel G *et al*. Neuropsychological impairment among former microelectronics workers. Neurotoxicology 1991;12:87-104

Bowler RM, Mergler D, Rauch SS *et al*. Affective and personality disturbances among female former microelectronics workers. Journal of Clinical Psychology 1991;47(1):41-52

Bowler RM, Mergler D, Rauch SS *et al*. Stability of psychological impairment: two year follow-up of former microelectronic workers' affective and personality disturbance. Women and Health 1992;18(3):27-48

Brackbill RM, Maizlish N and Fischbach T. Risk of neuropsychiatric disability among painters in the United States. Scandinavian Journal of Work, Environment and Health June 1990;16(3):182-188

Broadwell DK, Darcey DJ, Hudnell HK *et al*. Work-site clinical and neurobehavioural assessment of solvent-exposed microelectronics workers. American Journal of Industrial Medicine 1995;27(5):677-698

Bruhn P, Arlien-Soborg P, Gyldensted C *et al*. Prognosis in chronic toxic encephalopathy. A two-year follow-up study in 26 house painters with occupational encephalopathy. Acta Neurologica Scandinavica 1981;64(4):259-272

Chen R, Dick F and Seaton A. Health effects of solvent exposure among dockyard painters: mortality and neuropsychological symptoms. Occupational and Environmental Medicine 1999(a);56(6):383-387

Chen R, Dick F, Semple S *et al*. Exposure to organic solvents and personality. Occupational and Environmental Medicine 2001;58(1):14-18

Chen R, Wei L, Seaton A. Neuropsychological symptoms in Chinese male and female painters: an epidemiological study in dockyard workers. Occupational and Environmental Medicine 1999(b);56(6):388-390

Cherry N, Hutchins H, Pace T *et al*. Neurobehavioural effects of repeated occupational exposure to toluene and paint solvents. British Journal of Industrial Medicine 1985;42(5):291-300

Cherry NM, Labrèche FP and McDonald JC. Organic brain damage and occupational solvent exposure. British Journal of Industrial Medicine 1992;49:776-781

Chia SE, Ong CN, Poon WH *et al*. Neurobehavioural effects on workers in a video tape manufacturing factory in Singapore. Neurotoxicology 1993 14(1):51-56

Colvin M, Myers J, Nell V *et al*. A cross-sectional survey of neurobehavioural effects of chronic solvent exposure on workers in a paint manufacturing plant. Environmental Research 1993;63(1):122-132

Condray R, Morrow LA, Steinhauer SR *et al*. Mood and behavioural symptoms in individuals with chronic solvent exposure. Psychiatry Research 2000;97(2-3):191-206

Crossen JR and Wiens AN. Wechsler memory scale - revised: Deficits in performance associated with neurotoxic solvent exposure. The Clinical Neuropsychologist 1988;2(2):181-187

Daniell W, Stebbins A, O'Donnell J *et al*. Neuropsychological performance and solvent exposure among car body repair shop workers. British Journal of Industrial Medicine 1993;50(4):368-377

Daniell WE, Claypoole KH, Checkoway H *et al*. Neuropsychological function in retired workers with previous long term occupational exposure to solvents. Occupational and Environmental Medicine 1999;56(2):93-105

Department for Work and Pensions. Conditions due to chemical agents: Report by the Industrial Injuries Advisory Council in accordance with Section 171 of the Social Security Administration Act 1992 reviewing the prescription of conditions due to chemical agents. Social Security Administration Act 1992 Cm 5395 Feb 2002

Derogatis L. SCL-90 administration, scoring and procedures manual-II. Towson, MD. Clinical Psychometric Research 1983

Dryson EW and Ogden JA. Organic solvent induced chronic toxic encephalopathy: extent of recovery, and associated factors, following cessation of exposure. Neurotoxicology 2000 Oct;21(5):659-665

Edling C, Ekberg K, Ahlborg Jr G. *et al*. Long term follow up of workers exposed to solvents. British Journal of Industrial Medicine 1990;47(2):75-82

Ekberg K, Barregard L, Hagberg S *et al*. Chronic and acute effects of solvents on central nervous system functions in floorlayers. British Journal of Industrial Medicine 1986 Feb;43(2):101-106

Ellingsen DG and Lorentzen P. A neuropsychological study of patients exposed to organic solvents. International Journal of Occupational and Environmental Health 1997 Jul/Sep;3(3):177-183

Elofsson SA, Gamberale F, Hindmarsh T *et al*. Exposure to organic solvents: A cross-sectional epidemiologic investigation of exposed car and industrial spray painters with reference to the nervous system. Scandinavian Journal of Work, Environment and Health 1980;6:239-273

Escalona E, Yanes L, Feo O *et al*. Neurobehavioural evaluation of Venezuelan workers exposed to organic solvent mixtures. American Journal of Industrial Medicine 1995;27(1):15-27

European Commission. 1997. Occupational exposure limits. Key document. Criteria for the qualitative evaluation of human neurobehavioural studies of neurotoxicity. European Commission Report EUR 17390 EN

Eysenck HJ and Eysenck SBJ. 1991. Manual of the Eysenck Personality Scales (EPS adult) London. Hodder & Stoughton.

Fidler AT, Baker EL and Letz RE. Neurobehavioural effects of occupational exposure to organic solvents among construction painters. British Journal of Industrial Medicine 1987;44(5):292-308

Foo SC, Lwin S, Chia SE *et al*. Chronic neurobehavioural effects in paint formulators exposed to solvents and noise. Annals Academy of Medicine, Singapore 1994;23(5):650-654

French LR, Schuman LM, Mortimer JA *et al*. A case-control study of dementia of the Alzheimer type. American Journal of Epidemiology 1985; 121(3):414-419

Friis L and Norbaeck D. Occurrence of neurpsychiatric symptoms at low levels of occupational exposure to organic solvents and relationships to health, lifestyle and stress. International Journal of Occupational and Environmental Health Jul/Sep 1997;3(3):184-189

Gade A, Mortensen EL, Bruhn P. Chronic painter's syndrome. A reanalysis of psychological test data in a group of diagnosed cases, based on comparisons with matched controls. Acta Neurologica Scandinavica 1988 Apr;77(4):293-306

Goldberg D. 1978. Manual of the General Health Questionnaire. Windsor; NFER-Nelson

Gregersen P, Angelso B, Nielsen TE *et al*. Neurotoxic effects of organic solvents in exposed workers: an occupational, neuropsychological and neurological investigation. American Journal of Industrial Medicine 1984;5(3):201-205

Gregersen P, Klausen H and Elsnab CU. Chronic toxic encephalopathy in solvent-exposed painters in Denmark 1976-1980: Clinical cases and social consequences after a 5-year follow-up. American Journal of Industrial Medicine 1987;11(4):399-417

Grosch JW, Neale AV and Demers RY. Neurobehavioural and health-related deficits in solvent-exposed painters. American Journal of Industrial Medicine 1996;30(5):623-632

Gubéran E, Usel M, Raymond L *et al*. Disability, mortality and incidence of cancer among Geneva painters and electricians: a historical prospective study. British Journal of Industrial Medicine 1989;46:16-23

Gupta BN, Kumar P and Srivastava AK. An investigation of the neurobehavioural effects on workers exposed to organic solvents. Journal of the Society of Occupational Medicine 1990;40(3):94-96

Hakkola M. Neuropsychological symptoms among tanker drivers with exposure to solvents. Occupational Medicine 1994;44(5):243-246

Hane M, Axelson O, Blume J *et al*. Psychological function changes among house painters. Scandinavian Journal of Work, Environmental and Health 1977;3:91-99

Hanninen H, Antti-Poika M, Juntunen J *et al*. Exposure to organic solvents and neuropsychological dysfunction: a study on monozygotic twins. British Journal of Industrial Medicine 1991;48(1):18-25

Hanninen H, Eskelinen L, Husman KAJ *et al*. Behavioral effects of long-term exposure to a mixture of organic solvents. Scandinavian Journal of Work, Environment and Health 1976;2(4):240-255

Haruna AY, Ohaeri JU, Lawal RA *et al*. Comparative study of psychiatric morbidity among workers at a paint factory in Nigeria. East African Medical Journal 1998;75(1):4-10

Hathaway SR and McKinley JC. A multiphasic personality schedule (Minnesota): I. Construction of the schedule. Journal of Psychology 1940;10:249-254

Heyman A, Wilkinson WE, Stafford A *et al*. Alzheimer's Disease: A study of epidemiological aspects. Annals of Neurology April 1984;15(4):335-341

Hogstedt C, Andersson K and Hane M. 1984. A questionnaire approach to the monitoring of early disturbances in central nervous functions. In R Aitio, K Riihimaki and H Vainio(eds) Biological monitoring and surveillance of workers exposed to chemicals. Washington Hemisphere

Hooisma J, Hanninen H, Emmen HH *et al*. Behavioral effects of exposure to organic solvents in Dutch painters. Neurotoxicology and Teratology 1993;15(6):397-406

Husman K. Symptoms of car painters with long-term exposure to a mixture of organic solvents. Scandinavian Journal of Work, Environment and Health 1980;6:19-32

Iregren A. Effects of Industrial Solvent Interactions: Studies of behavioral effects in man. Arbete Och Hälsa 1986:11.

Johnson BL, Baker EL , El Batawi M *et al* (eds). Prevention of neurotoxic illness in working populations. New York: John Wiley and Sons; 1987

Kilburn KH. Neurobehavioural and respiratory findings in jet engine repair workers: A comparison of exposed and unexposed volunteers. Environmental Research 1999;80(3):244-252

Kilburn KH and Warshaw RH. Neurobehavioural effects of formaldehyde and solvents on histology technicians: repeated testing across time. Environmental Research 1992;58(2):134-146

Kishi R, Harabuchi I, Katakura Y *et al*. Neurobehavioural effects of chronic occupational exposure to organic solvents among Japanese industrial painters. Environmental Research 1993;62(2):303-313

Kraut A, Lilis R, Marcus M *et al*. Neurotoxic effects of solvent exposure on sewage treatment workers. Archives of Environmental Health 1988 Jul-Aug;43(4):331-334

Kukull WA, Larson EB, Bowen JD *et al*. Solvent exposure as a risk factor for Alzheimer's disease: A case-control study. American Journal of Epidemiology 1995;141(11):1059-1071

Labrèche FP, Cherry NM and McDonald JC. Psychiatric-disorders and occupational exposure to solvents. British Journal of Industrial Medicine 1992;49(12):820-825

Lee DH, Kim JH, Lee YH *et al*. Neurobehavioural changes in shoe manufacturing workers. Neurotoxicology and Teratology 1998;20(3):259-263

Lee Se-Hoon and Lee Seung Han. A study on the neurobehavioural effects of occupational exposure to organic solvents in Korean workers. Environmental Research 1993;60(2):227-232

Lindgren M, Osterberg K, Orbaek P *et al*. Solvent-induced toxic encephalopathy: Electrophysiological data in relation to neuropsychological findings. Journal of Clinical and Experimental Neuropsychology 1997;19(5):772-783

Lindström K. Changes in psychological performances of solvent-poisoned and solvent-exposed workers. American Journal of Industrial Medicine 1980;1(1):69-84

Lindström K and Wickstrom G. Psychological function changes among maintenance house painters exposed to low levels of organic solvent mixtures. Acta Psychiat. Scand. 1983;67(303):81-91

Lindström K, Riihimaki H, Hanninen K. Occupational solvent exposure and neuropsychiatric disorders. Scandinavian Journal of Work, Environment and Health Oct 1984;10(5):321-323

Linz DH, De Garmo PL, Morton WE *et al*. Organic solvent-induced encephalopathy in industrial painters. Journal of Occupational Medicine 1986;28(2):119-125

LoSasso GL, Rapport LJ, Axelrod BN. Neuropsychological symptoms associated with low-level exposure to solvents and (meth) acrylates among nail technicians. Neuropsychiatry, Neuropsychology and Behavioural Neurology 2001;14(3):183-189

LoSasso GL, Rapport LJ, Axelrod BN *et al*. Neurocognitive sequelae of exposure to organic solvents and (meth) acrylates among nail-studio technicians. Neuropsychiatry, Neuropsychology and Behavioural Neurology 2002;15(1):44-55

Lundberg I, Gustavsson A, Hogberg M *et al*. Diagnoses of alcohol abuse and other neuropsychiatric disorders among house painters compared with house carpenters. British Journal of Industrial Medicine 1992;49(6):409-415

Lundberg I, Michelsen H, Nise G *et al*. Neuropsychiatric function of housepainters with previous long-term heavy exposure to organic solvents. Scandinavian Journal of Work, Environment and Health 1995;21(1):1-44

Maizlish NA, Langolf GD, Whitehead LW *et al*. Behavioural evaluation of workers exposed to mixtures of organic solvents. British Journal of Industrial Medicine 1985;42(9):579-590

McNair DM, Lorr M and Droppleman LF. Editis manual for the Profile of Mood States (Rev. ed). San Diego, CA: Educational and Industrial Service, 1992

Mikkelsen S. A cohort study of disability pension and death among painters with special regard to disabling presenile dementia as an occupational disease. Scandinavian Journal of Social Medicine 1980;16:34-43

Mikkelsen S, Jorgensen M, Browne E *et al*. Mixed solvent exposure and organic brain damage: A study of painters. Acta Neurologica Scandinavica 1988;118:1-143

Milanovic L, Spilich G, Vucinic G *et al*. Effects of occupational exposure to organic solvents upon cognitive performance. Neurotoxicology and Teratology 1990;12(6):657-660

Morrow LA, Gibson C, Bagovich GR *et al*. Increased incidence of anxiety and depressive disorder in persons with organic solvent exposure. Psychosomatic Medicine 2000;62: 746-750

Morrow LA, Kamis H and Hodgson MJ. Psychiatric symptomatology in persons with organic solvent exposure. Journal of Consulting and Clinical Psychology 1993;61(1):171-174

Morrow LA, Robin N, Hodgson MJ *et al*. Assessment of attention and memory efficiency in persons with solvent neurotoxicity. Neuropsychologia 1992;30(10):911-922

Morrow LA, Ryan CM, Hodgson MJ *et al*. Alterations in cognitive and psychological functioning after organic solvent exposure. Journal of Occupational Medicine 1990:32(5):444-450

Morrow LA, Ryan CM, Goldstein G *et al*. A distinct pattern of personality disturbance following exposure to mixtures of organic solvents. Journal of Occupational Medicine 1989;31(9):743-746

Morrow LA, Stein L, Bagovich GR *et al*. Neuropsychological assessment, depression and past exposure to organic solvents. Applied Neuropsychology 2001;8(2):65-73

Morrow LA, Steinhauer SR, Condray R *et al*. Neuropsychological performance of journeymen painters under acute solvent exposure and exposure-free conditions. Journal of the International Neuropsychological Society 1997;3:269-275

Muijser H, Geuskens RBM, Hooisma J *et al*. Behavioural effects of exposure to organic solvents in carpet layers. Neurotoxicology and Teratology 1996;18(4):455-462

Myers JE, Nell V, Colvin M *et al*. Neuropsychological function in solvent-exposed South African paint makers. Journal of Occupational and Environmental Medicine 1999;41(11):1011-1018

Nasterlack M, Dietz MC, Frank KH *et al*. A multidisciplinary cross-sectional study on solvent-related health effects in painters compared with construction workers. International Archives of Occupational and Environmental Health 1999;72(4):205-214

Nelson NA, Robins TG, White RF *et al*. A case-control study of chronic neuropsychiatric disease and organic solvent exposure in automobile assembly plant workers. Occupational and Environmental Medicine 1994;51(5):302-307

Ng TP, Lim LC, Win KK. An investigation of solvent-induced neuro-psychiatric disorders in spray painters. Annals of the Academy of Medicine, Singapore 1992 Nov;21(6):797-803

Ng TP, Ong SG, Lam WK *et al*. Neurobehavioural effects of industrial mixed solvent exposure in Chinese printing and paint workers. Neurotoxicology and Teratology 1990;12(6):661-664

Nijem K, Kristensen P, al-Khatib A *et al*. Prevalence of neuropsychiatric and mucous membrane irritation complaints among Palestinian shoe factory workers exposed to organic solvents and plastic compounds. American Journal of Industrial Medicine Aug 2001;40(2):192-198

Nordling Nilson L, Sällsten G, Hagberg S *et al*. Influence of solvent exposure and aging on cognitive functioning: an 18 year follow up of formerly exposed floor layers and their controls. Occupational and Environmental Medicine 2002;59(1):49-57

O'Donnell WE, DeSoto CB and DeSoto JL. Validity and reliability of the revised Neuropsychological Impairment Scale (NIS). Journal of Clinical Psychology 1993;49:372-382

O'Flynn RR, Monkman SM and Waldron HA. Organic solvents and presenile dementia: a case referent study using death certificates. British Journal of Industrial Medicine 1987;44:259-262

Olsen J, Sabroe S. A case-reference study of neuropsychiatric disorders among workers exposed to solvents in the Danish wood and furniture industry. Scandinavian Journal of Social Medicine Supp 1980;16:44-49

Orbaek P, Risberg J, Rosen I *et al*. Effects of long-term exposure to solvents in the paint industry. A cross-sectional epidemiologic study with clinical and laboratory methods. Scandinavian Journal of Work, Environment and Health 1985;11 supp 2:1-28

Parkinson DK, Bromet EJ, Cohen S *et al*. Health effects of long-term solvent exposure among women in blue-collar occupations. American Journal of Industrial Medicine 1990;17(6):661-675

Pauling TL and Ogden JA. Screening and neuropsychological assessment of spray painters at risk for organic solvent neurotoxicity. International Journal of Occupational and Environmental Health 1996 Oct/Dec;2(4):286-293

Rasmussen K and Sabroe S. Neuropsychological symptoms among metal workers exposed to halogenated hydrocarbons. Scandinavian Journal of Social Medicine 1986;14(3):161-168

Rasmussen K, Jeppesen HJ, Sabroe S. Solvent-induced chronic toxic encephalopathy. American Journal of Industrial Medicine 1993;23(5):779-792

Rasmussen H, Olsen J and Lauritsen J. Risk of encephalopathia among retired solvent-exposed workers: A case-control study among males applying for nursing home accommodation or other types of social support facilities. Journal of Occupational Medicine 1985; 27(8):561-566

Ratzon NZ, Derazne E and Sculsky M. Part II: The effect of long-term exposure to organic solvents on sensory-motor skills: A cross sectional study. Work 1999;12(2):159-164

Reinvang I, Borchgrevink HM, Aaserud O *et al*. Neuropsychological findings in a non-clinical sample of workers exposed to solvents. Journal of Neurology, Neurosurgery and Psychiatry 1994;57(5):614-616

Ridgway P. Organic solvent neuropathy: A review of the evidence for and against organic solvents in general having the ability to produce pathological effects detectable by neuroimaging, neurophysiology or histopathology in the nervous system of occupationally exposed people. Journal of Food and Chemical Toxicology 2002; In Press

Riise T and Moen BE. A nested case-control study of disability pension among seamen, with special reference to neuropsychiatric disorders and exposure to solvents. Neuroepidemiology 1990;9(2):88-94

Ruijten MWMM, Hooisma J, Brons JT *et al*. Neurobehavioural effects of long-term exposure to xylene and mixed organic solvents in shipyard spray painters. Neurotoxicology 1994;15(3):613-620

Ryan CM, Morrow LA, Hodgson M. Cacosmia and neurobehavioural dysfunction associated with occupational exposure to mixtures of organic solvents. American Journal of Psychiatry 1988;145(11):1442-1445

Saretto G, Oliveira FC, Kato M *et al*. Exposure to organic solvents and its effects on the central nervous system in workers of the Camacari petrochemical complex in Brazil. G Ital Med Lav Erg 1997;19(3):66-71

Seeber A, Demes P, Golka K *et al*. Subjective symptoms due to solvent mixtures, dioxin, and toluene: impact of exposure versus personality factors. Neurotoxicology 2000;21(5):677-684

Seppäläinen AM, Lindstrom K and Martelin T. Neurophysiological and psychological picture of solvent poisoning. American Journal of Industrial Medicine 1980;1:31-42

Shalat SL, Seltzer B and Baker EL. Occupational risk factors and Alzheimer's disease: A case-control study. Journal of Occupational Medicine 1988; 30(12):934-936

Spurgeon A. The validity and interpretation of neurobehavioural data obtained in studies to investigate the neurotoxic effects of occupational exposure to mixtures of organic solvents. The feasibility of a benchmarking approach to interpretation. Feb 2001; Health and Safety Executive Contract Research Report 355/2001 (http://www.hse.gov.uk/).

Spurgeon A, Glass DC, Calvert IA *et al*. Investigation of dose related neurobehavioural effects in paintmakers exposed to low levels of solvents. Occupational and Environmental Medicine 1994;51(9):626-630

Spurgeon A, Gompertz D and Harrington JM. Modifiers of non-specific symptoms in occupational and environmental syndromes. Occupational and Environmental Medicine 1996;53:361-366

Spurgeon A, Gray CN, Sims J *et al*. Neurobehavioural effects of long-term occupational exposure to organic solvents: Two comparable studies. American Journal of Industrial Medicine 1992;22(3):325-335

Struwe G, Knave B, Mindus P. Neuropsychiatric symptoms in workers occupationally exposed to jet fuel - a combined epidemiological and casuistic study. Act Psychiatrica Scandinavica Supp 1983;303:55-67

Triebig G and Hallermann J. Survey of solvent related chronic encephalopathy as an occupational disease in European countries. Occupational and Environmental Medicine 2001;58:575-581

Triebig G, Barocka A, Erbguth F *et al*. Neurotoxicity of solvent mixtures in spray painters: II Neurologic, psychiatric, psychological and neuroradiologic findings. International Archives of Occupational and Environmental Health 1992(a);64(5):361-372

Triebig G, Claus D, Csuzda I *et al*. Cross-sectional epidemiological study on neurotoxicity of solvents in paints and lacquers. International Archives of Occupational and Environmental Health 1988;60(4):233-241

Triebig G, Nasterlack M, Hacke W *et al*. Neuropsychiatric symptoms in active construction painters with chronic solvent exposure. Neurotoxicology 2000;21(5):791-794

Triebig G, Schaller KH and Welte D. Neurotoxicity of solvent mixtures in spray painters. I: Study design, workplace exposures and questionnaire. International Archives of Occupational and Environmental Health 1992(b);64:353-359

Tripathi SR, Bhattacharya SK and Kashyap SK. Neurobehavioural changes in workshop painters of a public transport network. Journal of Human Ergology 1995 Dec;24(2):153-160

Tripathi SR, Bhattacharya SK, Chattopadhya P *et al*. Neurobehavioural disturbances in workers engaged in high pressure spray painting. Journal of Human Ergology 1989;18(2):191-198

Tsai Song-Yen, Chen Jong-Dar, Chao Wen-Ying *et al*. Neurobehavioural effects of occupational exposure to low-level organic solvents among Taiwanese workers in paint factories. Environmental Research 1997;7(3):146-155

Tvedt B, Skyberg K and Berstad J. Chronic toxic encephalopathy among house painters with disability pension. Journal of the Oslo City Hospitals 1989 Jun-Jul;39(6-7):74-80

Valciukas JA, Lilis R, Singer RM *et al*. Neurobehavioural changes among shipyard painters exposed to solvents. Archives of Environmental Health 1985;40(1)47-52 Jan/Feb

van der Hoek JA, Verberk MM and Hageman G. Criteria for solvent-induced chronic toxic encephalopathy: a systematic review. International Archives of Occupational and Environmental Health 2000;73(6):362-368

van der Hoek JA, Verberk MM, van der Laan G *et al*. Routine diagnostic procedures for chronic encephalopathy induced by solvents: survey of experts. Occupational and Environmental Medicine 2001;58(6):382-385

van Vliet C, Swaen GM, Volovics A *et al*. Neuropsychiatric disorders among solvent-exposed workers. First results fro a Dutch case-control study. International Archives of Occupational and Environmental Health 1990;62(2):127-132

van Vliet C, Swaen GMH, Slangen JJM *et al*. The organic solvent syndrome: A comparison of cases with neuropsychiatric disorders among painters and construction workers. International Archives of Occupational and Environmental Health 1987;59(5):493-501

Wang JD and Chen JD. Acute and chronic neurological symptoms among paint workers exposed to mixtures of organic solvents. Environmental Research Apr 1993;61(1)107-116

Wechsler D. WAIS-III and WMS-III technical manual. San Antonio, TX: Psychological Corporation, 1997

White RF, Proctor SP, Echeverria D *et al*. Neurobehavioural effects of acute and chronic mixed-solvent exposure in the screen printing industry. American Journal of Industrial Medicine 1995;28(2):221-231

Williamson AM and Winder C. A prospective cohort study of the chronic effects of solvent exposure. Environmental Research 1993 Aug;62(2):256-271

Wing JK, Cooper JE and Sartorius N. The description and classification of psychiatric symptoms: An instruction manual for the PSE and CATEGO system. University Press, London, 1974

World Health Organization (1985). Chronic effects of organic solvents on the central nervous system and diagnostic criteria. WHO, Copenhagen (Environmental Health 5)

Zung WWK. A self-rating depression scale. Archives of Gen. Psychiatry 1965;12:63-70

Appendix 1

Appendix I

Databases searched

CISDOC

Producer:	International Occupational Safety and Health Information Centre (CIS) of the UN International Labour Organization (ILO)
Subject:	Occupational Safety and Health
Content:	Contains citations and abstracts to occupational health and safety literature published in over 35 countries

EMBASE

Producer:	Elsevier Science
Subject:	Biomedical and Pharmaceutical
Content:	Citations and abstracts to medical, nursing and psychiatric literature

HSELINE

Producer:	UK Health and Safety Executive (HSE) Information Services
Subject:	Occupational Health and Safety
Content:	Contains citations and abstracts of occupational health and safety literature both nationally and internationally. Also includes citations to all HSE and Health and Safety Commission (HSC) publications

MEDLINE

Producer:	US National Library of Medicine
Subject:	General medicine including occupational medicine
Content:	Citations and abstracts to world wide medical literature

NIOSHTIC US National Institute for Occupational Safety and Health (NIOSH)

Producer: NIOSH Technical Information Centre

Subject: Occupational Health and Safety

Content: Citations and abstracts to world wide health and safety literature

RILOSH [Ryerson International Labour Occupational Safety and Health Index]

Producer: Ryerson Technical University Library, Canada

Subject: Health and safety, labour relations, employment practices and personnel management topics

Content: Citations to articles in the area of health and safety and employment practices

SCIENCE CITATION INDEX

Producer: ISI Web of Science

Subject: Science

Content: Citations and abstracts to articles published in international journals in the field of science, medicine and psychiatry

SOCIAL SCIENCE CITATION INDEX

Producer: ISI Web of Science

Subject: Social science and humanities

Content: Citations and abstracts to articles published in international journals in the field of social science and humanities

Appendix II

Tables I - VII

Table I

Study details of neurobehavioural studies

KEY TO TABLE HEADINGS (in alphabetical order)				
C	Control Group		**I/E**	Inclusion/Exclusion Criteria
C/M	Confounders/Modifiers Controlled		**STC**	Standard Test Conditions
CLE	Control for Last Exposure		**TA**	Test Administration Type
E	Exposed Group			

KEY (in alphabetical order)				
A	all employees included		**Man**	manual
C	control group		**M/F**	both sexes
Comp	computer-administered		**NA**	not applicable
CS(1)	cross-sectional 1 group		**NS**	not stated
CS(2)	cross-sectional 2 or more groups		**R**	random
E	exposed group		**RS**	recruited by exposed subject
F	female		**S**	stratified
L	longitudinal		**V**	volunteers
M	male		*****	methodologically better studies

Principle Author (year)	Study Design	Occupation (exposed group)	Subject Selection Method	Response Rate	I/E	No: E	No: C	Sex	Age: E (years)	Age: C (years)	CLE	C/M	STC	TA
Hanninen (1976)	CS2	Car painters	S(E) NS(C)	98.5%(E)	Yes	100	101	NS	35($\bar{x}$)	matched within 1-2 years	NS	Age Job type Initial intelligence	NS	Man
Hane (1977)	CS2	House painters	R(E) NS(C)	NS	Yes	52	52	M	42.5($\bar{x}$) 25-60 (range)	matched within 1-2 years	NS	Age Job type Education Initial intelligence Alcohol	NS	Man
Elofsson (1980)	CS2	Car painters	S(E) NS(C)	83.7%(E) 61.0%(C1) 70.0%(C2)	Yes	80	(1)40 (2)40	NS	>25-65	matched	NS	Age Education Job type Employment status	NS	Man
Lindstrom (1983)	CS2	House painters	A(E) NS(C)	66.8(E) NS(C)	NS	219	229	NS	42.4($\bar{x}$)	41.9($\bar{x}$)	Yes	Age Education Initial intelligence Job type Alcohol Medication Geographical area	NS	Man
Gregersen (1984)	CS2	Painters Dry cleaners Boat builders Printers	NS	NS	Yes	61	29	M	39.7($\bar{x}$)	40.1($\bar{x}$)	Yes	Age Education Job type Alcohol Initial intelligence Head injury	NS	Man
Cherry (1985) *	CS2	Dockyard painters	A(E) NS(C)	74%(E) NS(C)	Yes	44	44	M	41.0($\bar{x}$)	40.8($\bar{x}$)	NS	Age Initial intelligence Education Alcohol Employment duration	Yes	Man
Maizlish (1985) *	CS2	Printers Spray painters	A(E) NS(C)	50%(E) 38%(C)	Yes	124	116	M/F	35($\bar{x}$) Total Group		Yes	Age Gender Education Job type Time of day Alcohol	Yes	Man

Principle Author (year)	Study Design	Occupation (exposed group)	Subject Selection Method	Response Rate	I/E	No: E	No: C	Sex	Age: E (years)	Age: C (years)	CLE	C/M	STC	TA
Ørbaek (1985)	CS2	Paint makers	A(E) NS(C)	90%(E) NS(C)	Yes	50	50	M	42($\bar{x}$) 27-65	Matched	NS	Age Education Weight Height Alcohol Smoking Mental health Medication Job type	NS	Man
Valciukas (1985)	CS2	Shipyard painters	NS	NS	NS	55	55	M/F	58.2($\bar{x}$)	58.3($\bar{x}$)	NS	Age Race Gender Education	NS	Man
Ekberg (1986)	CS2	Floor layers	R(E) R(C)	NS	Yes	(1) 25 (long exposure) (2) 25 (short exposure)	(1) 25 (long exposure) (2) 25 (short exposure)	M	(1) 46($\bar{x}$) (2) 29($\bar{x}$)	(1) 46($\bar{x}$) (2) 29($\bar{x}$)	NS	Age Employment duration Alcohol Job type	NS	Man
Iregren (1986) *	CS2	Painters	S(E) NS(C)	81%(E) 81%(C)	Yes	80	80	M	NS	NS	Yes	Age Initial intelligence Education Job type Employment status	NS	Man/ Comp
Fidler (1987) *	CS1	Construction painters	V	26.5%	Yes	101	NA	M	42.8($\bar{x}$)	NA	Yes	Age Education Initial intelligence Socio-economic status Alcohol Caffeine Blood lead Medication Injury Sleep loss	Yes	Comp

Principle Author (year)	Study Design	Occupation (exposed group)	Subject Selection Method	Response Rate	I/E	No: E	No: C	Sex	Age: E (years)	Age: C (years)	CLE	C/M	STC	TA
Baker (1988) *	CS1	Construction painters	V	37.1%	Yes	186	NA	M	40.0($\bar{x}$)	NA	Yes	Age Education Initial intelligence Socio-economic status Ethnic group Alcohol Test effort	Yes	Comp
Kraut (1988)	CS1	Sewage workers	A	86%	Yes	19	NA	M	43 (median) 24-62 (range)	NA	NS	Age Race Educational level	Yes	Man
Mikkelsen (1988) *	CS2	Painters	R(E) R(C)	89%(E) 82%(C)	Yes	85	85	M	53.9($\bar{x}$)	53.5($\bar{x}$)	Yes	Age Education Initial intelligence Job type Alcohol	NS	Man
Triebig (1988) *	CS2	House painters	R	NS	Yes	84	39	M	40($\bar{x}$)	44.6($\bar{x}$)	Yes	Age Initial intelligence Job type Socio-economic status	Yes	Comp
Tripathi (1989) *	CS2	Spray painters Degreasers	NS	NS	NS	45	25(1) 25(2)	M	32.4($\bar{x}$)	(1) 33.1($\bar{x}$) 25-40 (2) 32.8($\bar{x}$)	Yes	Age Initial intelligence Socio-economic status Alcohol Smoking Employment duration	Yes	Man
Gupta (1990) *	CS2	Varnishers	A(E) NS(C)	100%(E) NS(C)	Yes	(1) 30 (2) 15	25	NS	(1)33($\bar{x}$) (2)31.5($\bar{x}$)	34.5($\bar{x}$)	Yes	Age Education Job type Time of day	NS	Man
Milanovic (1990)	CS2	Industrial workers	NS(E) NS(C)	NS(E) NS(C)	Yes	23	23	M/F	41.4($\bar{x}$)	41.0($\bar{x}$)	Yes	Education Job type Alcohol Medication Socio-economic status	NS	Man

Principle Author (year)	Study Design	Occupation (exposed group)	Subject Selection Method	Response Rate	I/E	No: E	No: C	Sex	Age: E (years)	Age: C (years)	CLE	C/M	STC	TA
Ng (1990) *	CS2	Painters Paint makers Spray painters	A(E) NS(C)	86%(E) 92%(C)	Yes	78	145	M	33.3($\bar{x}$)	32.3($\bar{x}$)	Yes	Age Education Socio-economic status Alcohol Time of day	Yes	Man
Parkinson (1990) *	CS1	Microelectronic workers	R	77%	Yes	567	NA	F	43.7($\bar{x}$)	NA	NS	Age Education	Yes	Man
Bleeker (1991) *	CS1	Paint makers	A	91% 64% (2 sites)	NS	187	NA	M	42($\bar{x}$)	NA	Yes	Age Ethnic group Initial intelligence Alcohol Smoking Time of day	Yes	Man
Hanninen (1991) *	CS2	Twins	A (study pairs) R (reference pairs)	100% (study pairs) NS (reference pairs)	Yes	21 pairs	28 pairs	M/F	28-55 (study)	29-64 (referents)	Yes	Age	Yes	Man

Principle Author (year)	Study Design	Occupation (exposed group)	Subject Selection Method	Response Rate	I/E	No: E	No: C	Sex	Age: E (years)	Age: C (years)	CLE	C/M	STC	TA
Kilburn (1992)	L repeated testing	Histology technicians	V	NS	No	1x testing year 1: 104 year 2: 110 year 3: 53 year 4: 83 2x testing year 1: 47 year 2: 98 year 3: 91 year 4: 63 4x testing year 1: 19 year 2: 19 year 3: 19 year 4: 19		M/F	1x testing year 1: 40.4($\bar{x}$) year 2: 40.7($\bar{x}$) year 3: 37.5($\bar{x}$) year 4: 38 ($\bar{x}$) 2x testing year 1: 44 $\bar{x}$ year 2: 46.1 $\bar{x}$ year 3: 46.1 $\bar{x}$ year 4: 47.9 $\bar{x}$ 4x testing year 1: 46($\bar{x}$) year 2: 47($\bar{x}$) year 3: 49($\bar{x}$) year 4: 50($\bar{x}$)		NS	Age Education	NS	Man
Ng (1992)	CS2	Spray painters	A(E) NS(C)	100% (E) 100% (C)	Yes	15	15	M	30.8($\bar{x}$) 22-42 (range)	34.2($\bar{x}$) 26-41 (range)	NS	Age Education Job type Time of day	NS	Man

Principle Author (year)	Study Design	Occupation (exposed group)	Subject Selection Method	Response Rate	I/E	No: E	No: C	Sex	Age: E (years)	Age: C (years)	CLE	C/M	STC	TA
Spurgeon (1992) *	CS2	(1) Painters	A(E) R(C)	67%(E) NS(C)	Yes	90	90	M	21-65 (range)	21-65 (range)	Yes	Age Education Alcohol Initial intelligence Job type Medication Viral infection Sleep loss Computer experience Time of day	Yes	Comp
	CS2	(2) Painters Spray painters Printers Coach trimmers Degreasers Boat builders	A(E) R(C)	95%(E) NS(C)	Yes	144	144	M	21-65 (range)	21-65 (range)	Yes	Age Education Alcohol Initial intelligence Job type Medication Viral infection Sleep loss Computer experience Time of day	Yes	Comp
Triebig (1992)(a)	CS2	Spray painters	A(E) NS(C)	72%(E) NS(C)	Yes	83	42	M	44.2($\bar{x}$)	40.5($\bar{x}$)	Yes	Age Initial intelligence Job type Socio-economic status Alcohol Body mass index	NS	Man
Chia (1993) *	CS2	Videotape manufacturers	A(E) NS(C)	100%(E) NS(C)	Yes	19	26	M	30.7($\bar{x}$)	30.6($\bar{x}$)	Yes	Age Education Ethnic group Alcohol	Yes	Man

Principle Author (year)	Study Design	Occupation (exposed group)	Subject Selection Method	Response Rate	I/E	No: E	No: C	Sex	Age: E (years)	Age: C (years)	CLE	C/M	STC	TA
Colvin (1993) *	CS2	Paint makers	A(E) NS(C)	91%	Yes	43	24	M	48.0($\bar{x}$)	43.5($\bar{x}$)	NS	Age Education Alcohol Ethnic group Job type	Yes	Comp/ Man
Daniell (1993) *	CS1	Car body repair workers	A	60%	Yes	124	NA	M	(1)38.0($\bar{x}$) (2)36.3($\bar{x}$) (3)29.1($\bar{x}$) (4)29.0($\bar{x}$)	NA	Yes	Age Education Initial intelligence Alcohol Coffee Head injury Injury	Yes	Comp
Hooisma (1993) *	CS2	Painters	V(E) V(C)	51%(E)(1) 59.5%(C)(2) 29.8%(E)(1) 33.8%(C)(2)	Yes	(1) 47 (2) 45	(1) 53 (2) 43	M	(1)35.8($\bar{x}$) (2)63.2($\bar{x}$)	(1) 36.9($\bar{x}$) (2) 62.7($\bar{x}$)	NS	Age Initial intelligence Alcohol Job type	Yes	Comp/ Man
Kishi (1993)	CS2	Painters	NS(E) R(C)	NS	NS	20	20	M	39.5($\bar{x}$)	39.5($\bar{x}$)	NS	Age Education Initial intelligence Alcohol Smoking	NS	Man
Lee (1993)	CS2	Car painters Printers	V(E) V(C)	NS	NS	113	81	M	33.3($\bar{x}$)	34.7($\bar{x}$)	NS	Age Education Alcohol Smoking Job type	NS	Man
Rasmussen (1993) *	CS1	Degreasers drawn from historical cohort	A	85.3%	Yes	96 (81 currently employed)	NA	M	39.4($\bar{x}$)	NA	Yes	Age Initial intelligence Alcohol abuse	Yes	Man

Principle Author (year)	Study Design	Occupation (exposed group)	Subject Selection Method	Response Rate	I/E	No: E	No: C	Sex	Age: E (years)	Age: C (years)	CLE	C/M	STC	TA
Williamson (1993)	CS2 + L	Apprentice spray painters	NS	NS	NS	50	50	M	17.8($\bar{x}$)	18.2($\bar{x}$)	Yes	Age Education Ethnic group Smoking Alcohol Job type Employment duration	NS	Man + Comp
Foo (1994)	CS2	Paint makers	NS	NS	Yes	21	21	M	41.3($\bar{x}$) 27-53 (range)	40.8($\bar{x}$) 25-53 (range)	NS	Age Education Ethnic group Alcohol	NS	Man
Reinvang (1994)	CS2	Construction painters Degreasers Handlers of jet fuel	A(E) All matches (C)	NS	Yes	36	36	M	44.5($\bar{x}$)	44.1($\bar{x}$)	NS	Age Education Initial intelligence Job type	NS	Man
Ruijten (1994)	CS2	Shipyard spray painters	NS	NS	Yes	28	25	NS	38.6($\bar{x}$)	38.7($\bar{x}$)	NS	Age Education Gender Alcohol Job type	NS	Comp
Spurgeon (1994) *	CS2	Paint makers	R(E) R(C)	42%(E) NS(C)	Yes	110	110	M	NS	NS	Yes	Age Education Initial intelligence Job type Alcohol Smoking Job satisfaction Handedness Viral infection Sleep loss Computer experience	Yes	Comp

Principle Author (year)	Study Design	Occupation (exposed group)	Subject Selection Method	Response Rate	I/E	No: E	No: C	Sex	Age: E (years)	Age: C (years)	CLE	C/M	STC	TA
Bolla (1995) *	CS2	Paint makers	A(E) V(C)	76%(E) NS(C)	Yes	144	52	M	42($\bar{x}$) 31-63 (range)	45($\bar{x}$) 31-63 (range)	Yes	Age Education Initial intelligence Ethnic group Job type Alcohol Smoking	Yes	Man
Broadwell (1995)	CS2	Microelectronic workers	A(E) S(C)	71%(E) NS(C)	Yes	25	32	M/F	47.0($\bar{x}$)	47.6($\bar{x}$)	NS	Age Gender Education Ethnic group Alcohol Smoking Medication	NS	Man / Comp
Escalona (1995) *	CS2	Adhesive workers	NS	70%(E) 54%(C)	Yes	67	82	M/F	33($\bar{x}$)	30($\bar{x}$)	NS	Age Gender Education Job type	Yes	Man
Lundberg (1995) *	CS2	House painters	A(E) NS(C)	91%(E) 84%(C)	Yes	135	71	M	NS	NS	Yes	Age Education Initial intelligence Job type Alcohol Injury Medication Smoking Other exposure Vocational training Handedness	Yes	Man
Tripathi (1995) *	CS2	Paint sprayers	NS	NS	Yes	100	(1) 60 (2) 75	M	33.3($\bar{x}$)	(1) 33.2($\bar{x}$) (2) 33.3($\bar{x}$)	Yes	Age Education Socio-economic status Alcohol Smoking Employment duration	Yes	Man

Principle Author (year)	Study Design	Occupation (exposed group)	Subject Selection Method	Response Rate	I/E	No: E	No: C	Sex	Age: E (years)	Age: C (years)	CLE	C/M	STC	TA
White (1995) *	CS1 (2 years)	Printers	A	89% (year 1) 84% (year 2)	NS	30	NA	M/F	34($\bar{x}$)	NA	No	Age Gender Education	Yes	Man
Grosch (1996) *	CS2	Painters	V(E) V(C)	25%(E) NS(C)	NS	133	51	M/F	40.9($\bar{x}$)	56.0($\bar{x}$)	Yes	Age Initial intelligence Alcohol Smoking Job type	NS	Comp
Muijser (1996) *	CS2	Carpet layers	V(E) NS(C)	NS	Yes	77	71	M	35.5($\bar{x}$)	37.6($\bar{x}$)	Yes	Age Education Job type	Yes	Comp
Morrow (1997)	CS2	Painters	V(E) V(C)	NS	No	38	36	M/F	38($\bar{x}$)	35($\bar{x}$)	Yes	Age Job type Alcohol	NS	Man
Saretto (1997)	CS2	Petrochemical workers	NS	NS	NS	188	188	M	37.8($\bar{x}$)	38.6($\bar{x}$)	NS	Age Education Job type Alcohol	NS	Comp
Tsai (1997) *	CS2	Paint makers	A(E) NS(C)	68%(E) NS(C)	Yes	(1) 47 (2) 34 (3) 88	(1) 72 (2) 57	M/F	(1)37.9($\bar{x}$) (2)38.5($\bar{x}$) (3)38.9($\bar{x}$)	(1) 33.2($\bar{x}$) (2) 30.6($\bar{x}$)	Yes	Age Gender Education Alcohol Smoking Caffeine Socio-economic status Handedness Medication	NS	Comp
Lee (1998) *	CS2	Shoe makers	A(E) NS(C)	NS	Yes	40	28	F	48.0($\bar{x}$)	48.2($\bar{x}$)	Yes	Age Education Alcohol Smoking	Yes	Man
Daniell (1999) *	CS2	Retired painters and aerospace workers	A(E) R(C)	47-52% (over 3 groups)	Yes	(1) 67 (2) 22	126	M	62-74 (retired)	62-74 (retired)	Yes	Age Education Alcohol Job type	Yes	Man

Principle Author (year)	Study Design	Occupation (exposed group)	Subject Selection Method	Response Rate	I/E	No: E	No: C	Sex	Age: E (years)	Age: C (years)	CLE	C/M	STC	TA
Kilburn (1999)	CS2	Jet engine repairers	NS(E) RS(C)	NS	NS	154	112	M/F	42.7 ($\bar{x}$)	41.9 ($\bar{x}$)	NS	Age Sex Education Smoking	NS	Man
Myers (1999) *	CS1	Paint makers	A	NS	Yes	228	NA	M	46.0($\bar{x}$)	NA	Yes	Age Education Job type Alcohol Socio-economic status Race	Yes	Man
Nasterlack (1999) *	CS2	Construction painters	V(E) NS(C)	NS	Yes	366	193	M	41.7($\bar{x}$)	44.6($\bar{x}$)	NS	Age Education Job type Alcohol	NS	Man
Ratzon (1999)	CS2	Painters	A NS(C)	100% (E) NS (C)	Yes	31	31	M	45.03 ($\bar{x}$)	45.32 ($\bar{x}$)	NS	Age Education Country of origin		Comp
LoSasso (2002)	CS2	Nail studio technicians	NS(E) NS(C)	NS	Yes	33	35	F	32.0 ($\bar{x}$)	32.6 ($\bar{x}$)	NS	Age Education Ethnic group Initial intelligence Mental health Job type	NS	Man
Nordling Nilson (2002) *	L (2 groups)	Floor layers	R	81% (E + C)	Yes	41	40	M	Group 1 ≥55($\bar{x}$ 62) Group 2 40-50($\bar{x}$ 44)	Group 1 ≥55 ($\bar{x}$ 62) Group 2 40-50 ($\bar{x}$ 44)	Yes	Age Education Alcohol Job type Employment duration	Yes	Man

Table II

Exposures and outcomes in neurobehavioural studies

KEY (in alphabetical order)				
CS1	cross-sectional, 1 group		**NA**	not applicable
CS2	cross-sectional, 2 groups		**NS**	not stated
Cumulative	index combining duration and level		*	methodologically better studies
L	longitudinal			

Principle Author (year)	Occupational Group	Study Design	Solvents	Exposure Duration (years)	Basis for exposure index	No: of test outcomes	No: of outcomes showing difference between groups	No: of outcomes showing exposure-effect
Hanninen (1976)	Car painters	CS2	Toluene Xylene Butyl acetate White spirit MIBK Isopropanol Ethyl acetate Acetone Ethanol	(range 1 - >26)	-	19	6	No analysis
Hane (1977)	House painters	CS2	NS	14.2($\bar{x}$) 4-42 (range)	-	12	4	No analysis
Elofsson (1980)	Car painters	CS2	Toluene Xylene Styrene Ethanol Butanol Proponal Acetone MEK MIBK Acetates Methylene chloride Trichloroethylene Trichloroethane White spirit	NS	-	19	10	No analysis
Lindstrom (1983)	House painters	CS2	White spirit (others not specified)	22($\bar{x}$)	(1) Duration (2) Cumulative	8	2	1

Principle Author (year)	Occupational Group	Study Design	Solvents	Exposure Duration (years)	Basis for exposure index	No: of test outcomes	No: of outcomes showing difference between groups	No: of outcomes showing exposure-effect
Gregersen (1984)	Painters Printers Boat builders Dry cleaners	CS2	White spirit Styrene Toluene Perchloroethylene	12.9($\bar{x}$)	-	9	2	No analysis
Cherry (1985) *	Dockyard painters	CS2	White spirit Dichloromethane Trichloroethylene Methyl n-butyl ketone n-butanol	NS	Duration	12	0	0
Maizlish (1985) *	Printers Spray painters	CS2	Isopropanol Methylene chloride Trichloroethylene Acetone MEK Naptha Toluene Xylene Ethylbenzene Hexane	7($\bar{x}$)	Current exposure levels	9	1	0
Ørbaek (1985)	Paint makers	CS2	Acetone Butanol Butyl acetate White spirit MIBK Toluene Xylene	NS	-	14	1	No analysis

Principle Author (year)	Occupational Group	Study Design	Solvents	Exposure Duration (years)	Basis for exposure index	No: of test outcomes	No: of outcomes showing difference between groups	No: of outcomes showing exposure-effect
Valciukas (1985)	Shipyard painters	CS2	MIBK Xylene Perchloroethylene Ethylene glucol White spirit	(range 10< - >40)	Duration	3	2	0
Ekberg (1986)	Floor layers	CS2	Toluene Acetone Benzene Ethyl acetate	Group 1 27($\bar{x}$) Group 2 9($\bar{x}$)	(1) Duration (2) Cumulative	10	Group 1 1 Group 2 1	(1) 3 (2) 4
Iregren (1986) *	Painters	CS2	NS	NS	Duration	18	4	0
Fidler (1987) *	Construction painters	CS1	NS	17.9($\bar{x}$)	Cumulative (various)	10	NA	2
Baker (1988) *	Construction painters	CS1	NS	16.2($\bar{x}$) (range 0.3-47)	Cumulative	14	NA	1

Principle Author (year)	Occupational Group	Study Design	Solvents	Exposure Duration (years)	Basis for exposure index	No: of test outcomes	No: of outcomes showing difference between groups	No: of outcomes showing exposure-effect
Kraut (1988)	Sewage workers	CS1	Benzene Toluene	8.1($\bar{x}$) (range <1 – 37)	Duration	5	9/19 workers had abnormal result on at least 1 test compared to reference population n=715	Only workers with >9 years exposure had abnormal results
Mikkelsen (1988) *	Painters	CS2	White spirit	31 (median)	Cumulative (various)	9	1	Composite test score index
Triebig (1988) *	House painters	CS2	Ethylacetate Toluene Butylacetate Xylene Ethylbenzene MBK	≥ 10	Cumulative	11	0	0
Tripathi (1989) *	(1) Spray painters (2) Degreasers	CS2	(1) White spirit Xylene Other not specified (2) Diesel oil	(1) 10.53($\bar{x}$) (2) 10.80($\bar{x}$) (range 5-15)	Duration	8	0	4
Gupta (1990) *	Varnishers	CS2	Xylene Toluene	10.23($\bar{x}$)	Analysis consisted of unvariate comparison of scores of 3 groups (i) non-exposed (ii) occasionally exposed (iii) continuously exposed	5	5	4

Principle Author (year)	Occupational Group	Study Design	Solvents	Exposure Duration (years)	Basis for exposure index	No: of test outcomes	No: of outcomes showing difference between groups	No: of outcomes showing exposure-effect
Milanovic (1990)	Industrial workers (not specified)	CS2	MEK Toluene Cyclohexane Acetone	20.7($\bar{x}$)	-	15	4	No analysis
Ng (1990) *	Printers Paint makers Spray painters	CS2	Toluene Xylene Isopropanol Isobutanol Ethyl acetate Trichcloroethane Isophorone Acetone MEK MIBK	9.4($\bar{x}$) (range 1-41)	-	10	4	No analysis
Parkinson (1990) *	Microelectronic workers	CS1	Alcohol Acetone Xylene Benzene Trichloroethane Trichloroethylene	15.1($\bar{x}$)	Current exposure	8	0	0
Bleeker (1991) *	Paint makers	CS1	Toluene Xylene Other alipathic and aromatic hydrocarbons unspecified	15($\bar{x}$) (range < 1-36)	Cumulative	22	NA	5

Principle Author (year)	Occupational Group	Study Design	Solvents	Exposure Duration (years)	Basis for exposure index	No: of test outcomes	No: of outcomes showing difference between groups	No: of outcomes showing exposure-effect
Hanninen (1991) *	Various (twin study)	CS2	Various including Toluene Xylene Benzene Trichloroethylene Trichloroethanol Methylene chloride	High exposed range 3-26 10 (median) Low exposed range 8-26 19(median)	-	20	3	No analysis
Kilburn (1992)	Histology technicians	L (re-testing over 4 years)	Formaldehyde Xylene Toluene	NS	-	10	0	No analysis
Ng (1992)	Spray painters	CS2	Toluene Xylene MEK Ethyl acetate Ethylene glycol Isopropanol	9.4($\bar{x}$) 5-15 (range)	-	15	1	No analysis
Spurgeon (1992) *	(1) Painters (2) Painters Paint sprayers Printers Coach trimmers Boat builders Degreasers	CS2	(1) Toluene Xylene White spirit (2) NS	(1) 1 - >30 (range) (2) 1 - >30 (range)	(1) Duration (2) Duration	(1) 4 (2) 6	1 3	1 1

Principle Author (year)	Occupational Group	Study Design	Solvents	Exposure Duration (years)	Basis for exposure index	No: of test outcomes	No: of outcomes showing difference between groups	No: of outcomes showing exposure-effect
Triebig (1992)(a)	Spray painters	CS2	Toluene Xylenes Ethylbenzene Trimethylbenzene Aliphatic hydrocarbons Acetates (from Triebig 1992b)	(range 10-44)	Cumulative	7	0	0
Chia (1993) *	Video tape manufacturers	CS2	MEK Cychlohexane Tetrahydrofuran Toluene	3.5($\bar{x}$)	Current exposure levels	7	3	0
Colvin (1993) *	Paint makers	CS2	MEK Benzene Trichloroethylene MIBK Toluene Butyl acetate Xylene Cellosolve acetate Isophorone White spirit	NS (all >5)	Cumulative	28	2	4
Daniell (1993) *	Car body repairer workers	CS1	MEK Xylene MIBK n-hexane	Former painters 5.6($\bar{x}$) Low exposed 8.8($\bar{x}$) High exposed 8.6($\bar{x}$)	Cumulative	14	NA	4

Principle Author (year)	Occupational Group	Study Design	Solvents	Exposure Duration (years)	Basis for exposure index	No: of test outcomes	No: of outcomes showing difference between groups	No: of outcomes showing exposure-effect
Hooisma (1993) *	Painters	CS2	NS	NS	Time spent painting in last 5 years (younger and older painters) and number of narcotic episodes (older painters)	33	5	1 (younger painters) 1 (older painters)
Kishi (1993)	Painters	CS2	Toluene Xylenes Mineral spirits Methanol Acetone MEK Methyl acetate Ethyl acetate n-hexane Trichloroethylene	$14.2(\bar{x})$ (range 1-43)	Duration	10	2	0
Lee (1993)	Car painters	CS2	Toluene Xylenes MEK Trichloroethylene Perchloroethylene n-hexane	$7.8(\bar{x})$	Duration	6	3	0
Rasmussen (1993) *	Degreasers	CS1	Trichloroethylene CFC 113 White spirit Other aliphatics unspecified Aromatics unspecified	< 1-11 (range)	Cumulative	15	Expressed as degree of "psycho-organic syndrome"	OR medium exposure = 5.6 high exposure = 11.2

Principle Author (year)	Occupational Group	Study Design	Solvents	Exposure Duration (years)	Basis for exposure index	No: of test outcomes	No: of outcomes showing difference between groups	No: of outcomes showing exposure-effect
Williamson (1993)	Apprentice spray painters	CS2 + 2 year follow-up	Benzene Toluene Xylene Trimethylbenzene Acetone MEK Cyclohexene n-butanol 150-butanol n-butylacetate	< 1 year	-	7	0 (+ 0 at follow-up)	No analysis
Foo (1994)	Paint makers	CS2	Isopropyl Acetone Ethyl acetate Benzene Toluene Xylenes White spirit	20.2($\bar{x}$) (range 7-39)	-	9	2	No analysis
Reinvang (1994) *	Construction painters Degreasers Jet fuel handlers	CS2	White spirit Other (not specified)	24.5($\bar{x}$)	-	17	6	No analysis
Ruijten (1994)	Shipyard spray painters	CS2	Xylene Trimethylbenzene Butanol White spirit	16.9($\bar{x}$)	Cumulative	9	4	2

Principle Author (year)	Occupational Group	Study Design	Solvents	Exposure Duration (years)	Basis for exposure index	No: of test outcomes	No: of outcomes showing difference between groups	No: of outcomes showing exposure-effect
Spurgeon (1994) *	Paint makers	CS2	White spirit Toluene Xylene MEK MIBK	1 - >30	(i) Duration (ii) Cumulative	8	1 (performance worse in controls)	0
Bolla (1995) *	Paint makers	CS2	Toluene Xylene MEK Butanol Propanol Esters	<10 - >18 (range)	Cumulative	15	7	1
Broadwell (1995)	Microelectronic workers	CS2	2-propanol Toluene Trichloroethane Methylene chloride Chlorophene Acetone Trichloroethylene Methanol Xylene	9.2($\bar{x}$) (range 3-18)	-	8	4	No analysis
Escalona (1995) *	Adhesive workers	CS2	Toluene Xylene Butane Heptane Hexane n-hexane Benzene	7($\bar{x}$) (more than 50% > 10)	Duration	8	4	4

Principle Author (year)	Occupational Group	Study Design	Solvents	Exposure Duration (years)	Basis for exposure index	No: of test outcomes	No: of outcomes showing difference between groups	No: of outcomes showing exposure-effect
Lundberg (1995) *	House painters	CS2	White spirit Toluene Xylene	NS	Cumulative	29	1	1
Tripathi (1995) *	Paint sprayers	CS2	White spirit Benzene Toluene Xylene	10.4($\bar{x}$)	-	5	3	No analysis
White (1995) *	Printers	CS1 (2 year L)	Toluene MEK Methylene chloride Diacetone alcohol	Group 1 < 10 years Group 2 ≥ 10 years	Cumulative	Year 1 11 Year 2 10	1	0 (no change over 2 years)
Grosch (1996) *	Painters	CS2	Mineral spirits Xylene Naptha Toluene Ketones	NS	Cumulative	9	4	1
Muijser (1996) *	Carpet layers	CS2	Toluene Cyclohexane Ethyl acetate Heptane	NS	Current exposure	5	0	0
Morrow (1997)	Painters	CS2	Toluene Xylenes Mineral spirits	NS	Cumulative	22	5	Composite of 6 tests (learning and memory)

Principle Author (year)	Occupational Group	Study Design	Solvents	Exposure Duration (years)	Basis for exposure index	No: of test outcomes	No: of outcomes showing difference between groups	No: of outcomes showing exposure-effect
Saretto (1997)	Petrochemical workers	CS2	Benzene n-hexane Cyclohexane Methanol Butyl alcohol Styrene	(range 11-20)	Duration	12	2	2
Tsai (1997) *	Paint makers	CS1	Toluene Xylene n-hexane MIBK n-butyl acetone	Group 1 6.99($\bar{x}$) Group 2 7.66($\bar{x}$)	Cumulative	11	NA	0
Lee (1998) *	Shoe makers	CS2	Toluene MEK n-hexane Cyclohexane Dichbroethylene Trichloroethylene Benzene Xylene	High exposure groups 3.1($\bar{x}$) 7.5($\bar{x}$) Low exposure groups 4.4($\bar{x}$) 0.7($\bar{x}$)	(i) Duration (ii) Cumulative	6	1	(i) 0 (ii) 1
Daniell (1999) *	Retired painters and aerospace workers	CS2	NS	Painters 37($\bar{x}$) (range 15-49) aerospace painters 31($\bar{x}$) (range 9-41.6)	Cumulative	29	4	1 (painters) 5 (aerospace painters)

Principle Author (year)	Occupational Group	Study Design	Solvents	Exposure Duration (years)	Basis for exposure index	No: of test outcomes	No: of outcomes showing difference between groups	No: of outcomes showing exposure-effect
Kilburn (1999)	Jet engine repairers	CS2	Trichloroethane Trichloroethylene Methanol	NS	-	7	4	No analysis
Myers (1999) *	Paint makers	CS1	MEK Benzene Trichloroethylene MIBK Toluene Butyl acetate Xylene Cellosolve Acetate Isophorone White spirit	13.5($\bar{x}$)	Cumulative	18	NA	0
Nasterlack (1999) *	Construction painters	CS2	NS	25.7($\bar{x}$) (range 10-46)	Cumulative	6	2 (painters better)	2
Ratzon (1999)	Painters	CS2	NS	18.06($\bar{x}$)	Cumulative	5	4	4
Lo Sasso (2002)	Nail-studio technicians	CS2	Toluene Formaldehyde acrylates	6.7($\bar{x}$) (range 2-24)	Cumulative	12	5	5
Nordling Nilson (2002) *	Floor layers	L (18 year follow-up)	Benzene Acetone Toluene Xylene	NS	Cumulative	10	0	5 in those >60 years

Table III

Studies (of active workers) reporting symptom data alongside neurobehavioural test data (more study details in Table I)

KEY (in alphabetical order)				
ANS	Autonomic Nervous System		**NTSS**	Neurotoxicity Symptom Scale
CNS	Central Nervous System		**POMS**	Profile of Mood States
GHQ	General Health Questionnaire		**PNS**	Peripheral Nervous System
HSC	Hopkins Symptom Checklist		**PSE**	Present State Evaluation
MMP1	Minnesota Multiphasic Personality Assessment		**Q16**	Orëbro Questionnaire – 16 items
NCTB	National Core Test Battery (WHO)		**SCL90**	Symptom Checklist – 90 items
NES	Neurobehavioural Evaluation System		**VAS**	Visual Analogue Scale
NS	Not stated		*****	Non-standardised measure

Principle Author (year)	Occupational Group	Measures Used	Exposure Duration (years)	Principle Findings
Hanninen (1976)	Car painters	Rorchach Personality Test	(range 1 - >26)	Exposed group significantly less prone to emotional reactions and expressions of hostility.
Elofsson (1980) also reported in Struwe (1983)	Car painters	(1) General Symptoms * (23 items) (2) Psychiatric Symptoms * (52 items) (3) Neurological Symptoms * (38 items)	NS	Significantly more symptoms reported in exposed group on all three questionnaires.
Lindstrom (1983)	House painters	Symptom Questionnaire * (32 items)	22($\bar{x}$)	Exposed group reported 4 symptoms significantly more frequently (forgetfulness, sensitisation, weakened sense of smell and dizziness).
Gregersen (1984)	Painters Dry cleaners Boat builders Printers	Symptom Questionnaire *	12.9($\bar{x}$)	Symptoms of "dementia" reported to be more common in exposed group (impaired memory, tiredness, irritability). No statistical analysis reported.
Ørbaek (1985)	Paint makers	(1) Symptoms * (CNS, PNS, Somatic) (2) Psychiatric * Symptoms	NS	Significantly higher frequency in exposed group of reporting (1) 3/10 CNS, 3/4 PNS and 3/6 somatic symptoms. (2) 14/28 psychiatric symptoms.
Valciukas (1985)	Shipyard painters	Symptom Questionnaire *	(range <10 - >40)	No significant findings
Ekberg (1986)	Floor layers	Q16	Group 1 27($\bar{x}$) Group 2 9($\bar{x}$)	No significant findings

Principle Author (year)	Occupational Group	Measures Used	Exposure Duration (years)	Principle Findings
Fidler (1987)	Construction painters	(1) Neurological symptoms * (2) Mood (NES)	17.9($\bar{x}$)	(1) Three neurological symptoms significantly associated with cumulative exposure, 12 others showed positive association. (2) No significant findings
Baker (1988)	Construction painters	Mood (NES)	16.2($\bar{x}$) (range 0.3-47)	Significant association with cumulative exposure index on all scales.
Kraut (1988)	Sewage workers	Not specified	8.1($\bar{x}$) (range <1 – 37)	14 or 19 workers complained of "CNS symptoms consistent with solvent exposure".
Triebig (1988)	House painters	(1) Well-being * (2) Personality change *	≥ 10	(1) No significant findings. (2) Significantly increased reporting of personality change in exposed group.
Tripathi (1989)	Spray painters Degreasers	Mood (VAS)	(1) 10.53($\bar{x}$) (2) 10.80($\bar{x}$) (range 5-15)	No chronic effects (acute only)
Ng (1990)	Painters Paint makers Spray painters	(1) Q16 (2) Neurological/neuropsychiatric symptoms *	9.4($\bar{x}$) (range 1-41)	(1) Exposed significantly higher score on Q16 ($\bar{x}$ 2.9 v 1.9) (2) Exposed higher frequency of reporting affective, sleep disturbance and ANS symptoms)
Parkinson (1990)	Microelectronic workers	Neurological Symptoms * Somatic Symptoms * HSC	15.1($\bar{x}$)	Exposed workers significantly more likely to report neurological and somatic symptoms than "never exposed" group but no exposure-effect relationship.
Bleeker (1991)	Paint makers	(1) PSE (2) Zung Depression Scale (3) Q16	15($\bar{x}$) (range < 1-36)	No significant findings

Principle Author (year)	Occupational Group	Measures Used	Exposure Duration (years)	Principle Findings
Kilburn (1992)	Histology technicians	Mood (POMS)	NS	No significant findings
Ng (1992)	Spray painters	Q16	9.4($\bar{x}$) 5-15 (range)	Significantly higher score in exposed subjects
Spurgeon (1992)	(a) Painters	(1) GHQ (2) Q16	<10 - >30	No significant findings
	(b) Painters Spray painters Printers Coach trimmers Degreasers Boat builders	(1) GHQ (2) Q16	<10 - >30	No significant findings for GHQ. Significantly higher symptom reporting on Q16 for exposed group ($\bar{x}$ 3.54 v 2.62).
Triebig (1992)	Spray painters	PSE	(range 10-44)	No significant findings
Chia (1993)	Video tape manufacturers	General Symptoms Questionnaire *	3.5($\bar{x}$)	Significantly higher prevalence of headache, eye and nose irritation in exposed group.
Colvin (1993)	Paint makers	General Symptoms Questionnaire *	Not specified (all >5)	No significant findings
Daniell (1993)	Car body repair workers	Mood (NES)	Former painters 5.6($\bar{x}$) Low exposed 8.8($\bar{x}$) High exposed 8.6($\bar{x}$)	No significant findings

Principle Author (year)	Occupational Group	Measures Used	Exposure Duration (years)	Principle Findings
Hooisma (1993)	Painters	(1) Mood (NES) (2) Mood (NCTB)	NS Exposure index calculated	No significant findings
Kishi (1993)	Painters	(1) Symptom Questionnaire * (61 items) (2) Mood POMS	14.2($\bar{x}$) (range 1-43)	(1) 7 symptoms reported more frequently in exposed group. No relationship with duration of exposure. (2) No significant findings
Reinvang (1994)	Construction painters Degreasers Jet fuel handlers	Mood (NES)	24.5($\bar{x}$)	No significant findings
Ruijten (1994)	Shipyard spray painters	Neurotoxic Symptom Checklist * (53 items)	16.9($\bar{x}$)	Significantly higher scores in exposed group for mood changes, equilibrium complaints and fatigue.
Spurgeon (1994)	Paint makers	GHQ	<11 - >30 (range)	No significant findings
Bolla (1995)	Paint makers	(1) PSE (2) Q16	NS Exposure index calculated	No significant findings
Broadwell (1995)	Microelectronic workers	(1) Mood (NES) (2) MMPI	9.2($\bar{x}$) (range 3-18)	Significantly higher total score in exposed group for both measures.
Escalona (1995)	Adhesive makers	Mood (POMS)	7($\bar{x}$) (more than 50% > 10)	Significant association with duration of exposure for 4 scales.

Principle Author (year)	Occupational Group	Measures Used	Exposure Duration (years)	Principle Findings
Lundberg (1995)	House painters	(1) Neuropsychiatric Symptoms * (2) Mood (POMS)	NS Exposure index calculated	(1) Significant association between frequency of reporting neuropsychiatric symptoms and cumulative exposure (2) No significant findings
White (1995)	Printers	Mood (POMS)	Group 1 < 10 years Group 2 ≥ 10 years	No significant findings
Grosch (1996)	Painters	Mood (NES)	NS	No significant findings
Morrow (1997)	Painters	SCL90	NS	Psychiatric symptomatology significantly higher in painters.
Saretto (1997)	Petrochemical workers	Mood (NCTB)	(range 11-20)	Significantly higher scores in exposed group on all five scales
Tsai (1997)	Paint makers	Mood (NES)	Group 1 6.99($\bar{x}$) Group 2 7.66($\bar{x}$)	No significant findings

Principle Author (year)	Occupational Group	Measures Used	Exposure Duration (years)	Principle Findings
Daniell (1999)	Retired painters and aerospace workers	(1) Beck Depression Inventory (2) diagnostic interview schedule *	Painters 37($\bar{x}$) (range 15-49) aerospace painters 31($\bar{x}$) (range 9-41.6)	Painters had a significantly higher score than referents on both measures but only three painters reached borderline scores for clinical depression.
Kilburn (1999)	Jet engine repairers	(1) Mood (POMS) (2) General symptoms *	NS	(1) Significantly higher total score for exposed subjects (2) Significantly higher frequency of reporting on all 35 symptoms for exposed subjects.
Nasterlack (1999)	Construction painters	(1) PSE (2) Q16 (3) NTSS	25.7($\bar{x}$) (range 10-46)	Significant increases in symptoms which were related to cumulative exposure on all three measures.

Table IV

Studies (of active workers) reporting psychiatric symptom data only (+ 1 study of retired non-patients)

KEY (in alphabetical order)				
A	All workforce		**NIS**	Neuropsychological Impairment Scale
C	Control group		**NS**	Not stated
CNS	Central Nervous System		**NTSS**	Neurotoxicity Symptom Scale
CPRS	Comprehensive Psychopathological Rating Scale		**POMS**	Profile of Mood States
CS1	Cross-sectional (1 group)		**PSE**	Present State Evaluation
CS2	Cross-sectional (2 groups)		**Q16**	Orëbro Questionnaire – 16 items
E	Exposed group		**R**	Random
EPI	Eysenck Personality Inventory		**S**	Stratified
F	Female		**V**	Volunteer
M	Male		**ZDI**	Zung Depression Inventory
M/F	Both sexes		*****	Non-standardised

Principle Author (Year)	Study Design	Study Population	Subject Selection Method	Response Rate	No: Exposed/ Control	Sex	Age (years) Exposed/ Control	Control/ Adjustment	Measures	Exposure Duration (years)	Principle Findings
Husman (1980)	CS2	Car painters	S(E) NS(C)	NS	102(E) 102(C)	M	35(E) ($\bar{x}$) 20-65(E) (range) matched(C)	Age Job type	Symptom questionnaire*	14.8($\bar{x}$) 1-40 (range)	Symptoms of fatigue, memory disturbance and vigilance reported significantly more often in exposed group
Struwe (1983)	CS2	Jet fuel handlers	Selected on basis of exposure	NS	30(E) 30(C1) 30(C2)	NS	46($\bar{x}$) (all groups)	Age Education Union activity Employment duration	(1) structured diagnostic interview * (2) CPRS	17.1($\bar{x}$) 4-32 (range)	Exposed subjects reported (i) significantly more medical consultations for depression and anxiety (ii) significantly more symptoms (CPRS) (iii) seven exposed subjects diagnosed with "mild organic brain syndrome"
Rasmussen (1986)	CS2	Degreasers	A(E) R(C)	78.3% (overall)	368(E) 94(C)	M/F	37.7(E) ($\bar{x}$) 38.5(C) ($\bar{x}$)	Age Alcohol Cerebral incident Other exposure	Q16 + other questions	7.3($\bar{x}$)	Prevalence OR of symptoms related to exposure Non-exposed 1.0 Present exposure light 0.96 Present exposure heavy 3.42 Previous exposure 4.22
Bolla (1990)	CS1	Paint makers	V	NS	187	M	42($\bar{x}$)	Age IQ Health status Alcohol	(1) ZDI (2) PSE (3) Q16	15($\bar{x}$) <1-36 (range)	No significant association between any of measures and cumulative exposure indices
Wang (1993)	CS1	Painters Spray painters Paint makers	R	NS	196	NS	Low exposure 29.7($\bar{x}$) High exposure 41.0($\bar{x}$)	Age Duration of employment Smoking	Q16	(1) 4.6($\bar{x}$) (2) 6.4($\bar{x}$) (3) 17.6($\bar{x}$)	High exposed group 3.9 times more likely to develop 3+ chronic CNS symptoms

Principle Author (Year)	Study Design	Study Population	Subject Selection Method	Response Rate	No: Exposed/ Control	Sex	Age (years) Exposed/ Control	Control/ Adjustment	Measures	Exposure Duration (years)	Principle Findings
Hakkola (1994)	CS2	Tanker drivers	A(E) NS(C)	NS	61(E) 56(C1) 31(C2)	M	<30 - >50 (range)	NS	1) general symptom questionnaire * 2) Mood (POMS)	NS	Higher % of general symptoms and fatigue, depression and hostility in tanker drivers (no statistical analysis)
Friis (1997)	CS1	Miners about to be redundant + community sample	A Miners R Community	68% Miners 54% Community	178	M/F	47.2($\bar{x}$) (both groups)	Variables in model: Age Gender Alcohol Smoking Unemployment Medication Chronic disease Musculoskeletal disease	Q16	2.3($\bar{x}$) <1-40 (range)	Symptom score significantly related to: Regular medication, OR 4.0 Years work with solvents, OR 2.2 Alcohol/month, OR 2.8 Unemployment, OR 2.4
Haruna (1998)	CS2	Paint makers	A(E) R(C1) R(C2)	100% (E) NS (C1) NS (C2)	60 (E) 60 (C1) 60 (C2)	M/F	38.1($\bar{x}$) 41.1($\bar{x}$) 37.7($\bar{x}$)	Socio-economic status	PSE (adapted)	13.3($\bar{x}$)	No difference between groups for total PSE scores Paint makers significantly higher scores for physical pain, tiredness and weight loss
Chen (1999)(a)	Nested CS2	Dockyard painters	A(E) R(C)	48.5% (E) 62% (C)	260(E) 539(C)	M	NS	Age Education Smoking Alcohol Social conformity	Q16 + other questions	1-41 (range)	RR for high symptom score increased with exposure: 1-4 years 2.27 5-9 years 2.42 10-14 years 2.89 15-41 years 3.41
Chen (1999)(b)	CS2	Dockyard painters	According to criteria(E) R(C)	94% (E) 97% (C)	116(E) 263(C)	M/F	NS	Age Education Smoking Alcohol Social conformity	Q16 + other questions	2-43 (range)	RR for high symptom score increased with exposure: 2-15 years 6.61 16-22 years 14.88 ≥22 years 9.42

Principle Author (Year)	Study Design	Study Population	Subject Selection Method	Response Rate	No: Exposed/ Control	Sex	Age (years) Exposed/ Control	Control/ Adjustment	Measures	Exposure Duration (years)	Principle Findings
Condray (2000)	CS2	Painters	A(E) V(C)	8.5%(E) 5.4%(C)	29(E) 32(C)	M	40.0(E) ($\bar{x}$) 37.0(C) ($\bar{x}$)	Age IQ Income Alcohol Medical conditions Ethnic group Recent exposure	Structured diagnostic interview *	17.3($\bar{x}$) 4-48 (range)	Significantly more painters diagnosed with adult lifetime incidence of major depressive disorder. Duration of solvent exposure significantly associated with interpersonal relationship difficulties
Seeber (2000)	CS1	Paint makers	NS	NS	40	M	40($\bar{x}$)	Trait anxiety Sensitivity Age Verbal intelligence	German scale (standardised) Trait Anxiety Sensitivity Scale	16($\bar{x}$)	Multivariate analysis shows that for symptom reporting trait anxiety explains more of variance than cumulative solvent exposure
Triebig (2000)	CS2	Painters	NS	NS	401(E) 209(C)	NS	41.7(E) ($\bar{x}$) 44.6(C) ($\bar{x}$)	Age Recent exposure Alcohol Education	(1) Q 16 + other questions (2) NTSS (3) PSE	25.7($\bar{x}$) 10-46 (range)	Significantly higher symptom scores in painters and significant correlations with cumulative exposure index for Q16 and NTSS
Chen (2001)	CS2	Dockyard painters	<u>UK</u> A(E) R(C) <u>Chinese</u> A(E) A(C)	<u>UK</u> 48.5% (E) 62% (C) <u>Chinese</u> 94% (E) 97% (C)	<u>UK</u> 260(E) 539(C) <u>Chinese</u> 116(E) 263(C)	<u>UK</u> M <u>Chinese</u> M/F	<u>UK</u> 35-96 (range) <u>Chinese</u> 30-82 (range)	Age Alcohol Education Smoking Social conformity	EPI (neuroticism scale)	1-41 (range)	Mean neuroticism scores for UK and Chinese painters significantly higher than for controls with significant exposure-response relationships ORs UK 1-4 years 2.03 5-9 years 2.38 10-14 years 7.05 15-41 years 1.76 ORs China 2-14 years 4.66 15-18 years 10.03 19-43 years 13.56

Principle Author (Year)	Study Design	Study Population	Subject Selection Method	Response Rate	No: Exposed/ Control	Sex	Age (years) Exposed/ Control	Control/ Adjustment	Measures	Exposure Duration (years)	Principle Findings
LoSasso (2001)	CS2	Nail studio technicians	NS	NS	150(E) 148(C)	F	32.3(E) ($\bar{x}$) 31.4(C) ($\bar{x}$)	Age Education Ethnic group	NIS	6.7($\bar{x}$) 2-24 (range)	Significantly higher level of symptom reporting in exposed group Significant association between symptoms and cumulative exposure
Nijem (2001)	CS1	Shoe makers	A	NS	167	M	29 (median)	Age Education Marital status Smoking	Q16 + general symptom questionnaire*	NS (>1)	Significant association between tingling in limbs and use of 2 solvents for cleaning for >24 months. Prevalence ratio 1.8

Table V

Case series

KEY (in alphabetical order)				
BAI	Beck Anxiety Inventory		**OM**	Occupational Medicine
BDI	Beck Depression Inventory		**POET**	Pittsburgh Occupational Exposure Test
BHI	Beck Hopelessness Inventory		**POMS**	Profile of Mood States
BSI	Brief Symptom Inventory		**PTSD**	Post-traumatic stress disorder
ED	Employment duration		**Q16**	Orëbro questionnaire – 16 items
ES	Employment status		**QLS**	Quality of Life Scale
EWS	Environmental Worry Scale		**SCL**	Symptom checklist (90 items)
F	Female		**SD**	Standard deviation
H-R	Halstead Reitan Neuropsychological Test Battery		**SES**	Socio-economic status
M	Male		**SLS**	Satisfaction with Life Scale
M/F	Both sexes		**WAIS-R**	Wechsler Adult Intelligence Scale - Revised
MMPI	Minnesota Multiphasic Personality Inventory		**WMS-R**	Wechsler Memory Scale - Revised
NA	Not applicable		*****	Non-standardised measure

Principle Author (Year)	Patients	Reference Group	Matching/ Adjustments	Age (years)	Sex	Exposure Duration (years)	Measures	Principle Findings
Arlien-Søborg (1979)	n=50 from 70 with suspected "organic solvent syndrome"	NA	NA	47($\bar{x}$) 24-63 (range)	M	27($\bar{x}$) 8-50 (range)	10 Neurobehavioural tests Symptoms*	39 patients diagnosed as intellectually impaired slight-moderate (25) moderate (11) moderate-severe (3) A range of CNS symptoms reported
Lindström (1980)	n=56 diagnosed with "organic solvent syndrome"	n=98 styrene exposed n=43 non-exposed	Age Job type	38.8($\bar{x}$) (patients) 29.5($\bar{x}$) (styrene exposed) 33.3($\bar{x}$) (non-exposed)	M	9.1($\bar{x}$) (patients)	WAIS-R (5 tests) Other (3 tests)	Significantly poorer performance in patients on 8 tests compared with styrene exposed and on 6 tests compared with non-exposed No association with cumulative exposure
Seppäläinen (1980)	n=107 diagnosed with solvent poisoning	NA	NA	M 35.8($\bar{x}$) F 42.0($\bar{x}$)	M 48 F 59	M 9.6($\bar{x}$) F 7.6($\bar{x}$)	WAIS-R	Significantly lower scores than standardisation sample in 4 tests (women) and 2 tests (men) Duration of exposure related to 2 tests in both sexes (but different tests)
Linz (1986)	n=15 industrial painters referred to OM clinic (pending litigation)	n=30 non-painters	Age Sex Educational level	24-56 (range)	M	<1-20	WAIS-R H-R MMP1 Other tests (2) Symptom questionnaire*	Painters had significantly higher prevalence of "neurasthenic" symptoms and of anxiety and depression. For most tests more than 16% of painters scored 1 SD below normative means
Crossen (1988)	n=20 sample of 52 already diagnosed with "toxic solvent encephalopathy"	NA	NA	46.9($\bar{x}$)	M	17.75($\bar{x}$)	WMS-R (5 tests)	Scores 1 SD below mean for all tests in those currently employed in non-exposed job (n=8) scored higher than unemployed (n=12)

Principle Author (Year)	Patients	Reference Group	Matching/ Adjustments	Age (years)	Sex	Exposure Duration (years)	Measures	Principle Findings
Ryan (1988)	n=17 history of solvent exposure and reported cognitive and affective changes	n=17 healthy non-exposed – controls from other study	Age Education	41.5($\bar{x}$) (patients) 41.7($\bar{x}$) (controls)	M	7.4($\bar{x}$) 1-18 (range)	WAIS-R WMS-R Other (4 tests)	No relationship between performance and duration of exposure Significant relationship with history of peak exposures on two tests
Berstad (1989)	n=17 diagnosed with "organic solvent syndrome" from 26 examined	NA	NA	49.2 ($\bar{x}$) 27-65 (range)	M 16 F 1	23.9 ($\bar{x}$) 1-45 (range)	WMS (2 tests) H-R (1 test) Other (2 tests)	16 diagnosed with encephalopathy (8 slight, 8 marked) 5 diagnosed with polyneuropathy (3 slight, 2 marked) Most impairment on tests of memory and spatiotactile functions
Morrow (1989)	n=22 history of solvent exposure	NA	NA	38($\bar{x}$) 27-61 (range)	M	7.3($\bar{x}$) <1-19 (range)	MMPI	Clinical significant profiles in 90% of group Similar profiles to war veterans with PTSD
Tvedt (1989)	n=14 1 had diagnosis of "solvent related encephalopathy" 13 had other diagnosis	NA	NA	61($\bar{x}$) 52-65 (range)	NS	29($\bar{x}$) 12-46 (range)	Q16 WAIS-R H-R	10 patients scored >4 on Q16 Median score of WAIS test with lowest result 1 SD below mean Concluded 5 patients had "solvent related encephalopathy"
Morrow (1990)	n=32 history of solvent exposure (10 involved in litigation)	n=32 healthy non-exposed volunteers controls from other study	Age Education	39.7($\bar{x}$) (patients) 40.1($\bar{x}$) (controls)	NS	9.0($\bar{x}$) <1-19 (range)	MMP1 WAIS (6 tests) Other (14 tests)	Significantly poorer performance in patients on 12 tests 4 MMP1 scales clinically elevated in patients History of peak exposures associated with 2 test scores Duration associated with 3 MMP1 scales

Principle Author (Year)	Patients	Reference Group	Matching/ Adjustments	Age (years)	Sex	Exposure Duration (years)	Measures	Principle Findings
Bowler (1991)	n=67 former microelectronic workers (in litigation)	n=67 healthy volunteers recruited by patients	Age Education Ethnic group Gender ES ED Alcohol Smoking	43.4($\bar{x}$) (patients) 43.5($\bar{x}$) (controls)	M/F	6.7($\bar{x}$)	WAIS-R (4 tests) WMS (18 tests) Other (10 tests)	Significant differences between the groups on 24 out of 32 tests No relationships between test outcomes and exposure duration
Bowler (1991)	n=70 former microelectronic workers awarded compensation	NA	NA	43.4($\bar{x}$)	F	7.1($\bar{x}$)	MMP1	85.7% of patients showed clinically elevated scores on at least one scale Predominant diagnosis somatoform 24.3% depression 15.7% anxiety 28.6% psychotic 14.3%
Morrow (1992)	n=40 diagnosis of 2A/2B solvent neurotoxicity	n=40 healthy non-exposed volunteers	Age Education	39.0($\bar{x}$) (patients) 37.2($\bar{x}$) (controls)	M/F	6.43($\bar{x}$) 1 day – 30 years	WAIS (1 test) WMS (2 tests) Other (3 tests)	Patients significantly lower performance on tests of memory and attention No relation with exposure duration or history of peak exposures
Morrow (1993)	n=30 history of solvent exposure	n=30 healthy non-exposed volunteers Controls for other study	Age Education SES	38.6($\bar{x}$) 25-55 (range) patients 38.6($\bar{x}$) 22-60 (range) controls	M/F	NS	SCL – 90 POMS BDI Self-concept scale Locus of control Hassles and uplifts scale	Patients scored significantly higher on 7 of 9 SCL scales, 4 of 5 POMS scales and BD1 No differences on other measures No relationship with cumulative exposure

Principle Author (Year)	Patients	Reference Group	Matching/ Adjustments	Age (years)	Sex	Exposure Duration (years)	Measures	Principle Findings
Ellingsen (1997)	n=42 from 190 with suspected "solvent-induced encephalopathy"	NA	NA	49.1($\bar{x}$) 28-64 (range)	M	24.6($\bar{x}$) 2-46 (range)	WAIS (6 tests) WMS (2 tests) H-R (3 tests) Other (7 tests)	Impairment of psychomotor function, memory and attention Significant association between psychomotor function and duration of exposure Moderate to severe impairment with at least 15 years exposure
Morrow (2000)	n=38 history of solvent exposure	n=37 healthy non-exposed volunteers	Age SES Education (higher in controls)	43.8($\bar{x}$) (patients) 40.1($\bar{x}$) (controls)	M/F	8.26($\bar{x}$) 1 day – 30 years (range)	Structured clinical interview	Significantly more of solvent exposed patients met criteria for DSM IV disorder – predominantly anxiety – (71% exposed 10% controls)
Bowler (2001)	n=265 selected randomly from 687 litigants (former munitions workers)	n=77 volunteers + friends of study group	Statistical adjustment for age, education, gender and ethnicity. Matched on smoking	56.6($\bar{x}$) (patients) 51.30($\bar{x}$) (controls)	F 172 M 93 (patients) F 42 M 35 (controls)	17.03($\bar{x}$) 3-38 (range)	WAIS (5 tests) WMS (8 tests) Other (9 tests) BS1 BAI BDI BHI POMS QLS SLS EWS	Significant differences between groups on 6 tests and on all measures of mood, psychiatric state and quality of life For African Americans only, significant test scores related to exposure duration No relation between exposure and mood or psychiatric measures for whites or African Americans
Morrow (2001)	n=38 history of solvent exposure	n=39 healthy non-exposed volunteers	Age SES	43.8($\bar{x}$) (patients) 40.2($\bar{x}$) (controls)	M/F	8.26($\bar{x}$) 1 day – 30 years (range)	POET (23 tests including parts of WAIS and WMS)	Significantly poorer scores in patients on tests of learning and memory, visuospatial abilities and psychomotor speed Associated with exposure duration for learning and memory

Table VI

Follow-up of cases of Chronic Toxic Encephalopathy (CTE)

KEY (in alphabetical order)

CNRS	Comprehensive Neuropsychiatric Rating Scale		**NS**	Not stated
CPRS	Comprehensive Psychcopathological Rating Scale		**SCL-90**	Symptom checklist (90 items)
MMPI	Minnesota Multiphasic Personality Inventory		**WHO/NCTB**	WHO National Core Test Battery

Principle Author (Year)	Characteristics of patients	Age (years)	Period of exposure (years)	Time to follow-up	Measures	Principle Findings
Bruhn (1981)	26 cases solvent-induced CTE (male painters) 16 receiving disability pensions	42($\bar{x}$) 24-63 (range)	28($\bar{x}$) 8-44 (range)	25 months($\bar{x}$) (22-31 months)	Symptoms 11 tests	No significant change in performance on any test. Slight improvement in symptoms in some patients
Antti-Poika (1982)	87 patients diagnosed with CTE	NS	NS	3-9 years	Symptoms	52% reported improvement in condition, 27% no change, 21% worse Younger patients with longer follow-up and no regular clinic check-ups improved most
Gregersen (1987)	21 cases solvent induced CTE (male painters) 18 had received disability compensation	44.8($\bar{x}$) 23-56 (range)	25.5($\bar{x}$) 6-40 (range)	5 years($\bar{x}$)	Symptoms 24 tests	12 patients scored as having slight-marked or marked intellectual impairment and 7 slight impairment. All reported symptoms of mild or severe intellectual impairment and constant fatigue. 29% reported severe irritability, 86% tearfulness and 24% headaches. 10 patients had failed to find other work having given up painting
Gade (1988)	20 cases of solvent-induced CTE. 6 had disability pension 12 had received compensation 20 non-exposed individually matched referents recruited from Department of Orthopaedic Surgery (mainly limb fractures)	28-63	24($\bar{x}$)	2 years	30 tests	Test results unchanged. Not significantly different from non-exposed controls after adjustment for age, education and initial intelligence Questions initial diagnosis
Edling (1990)	Initial diagnosis of mild solvent – induced CTE. Type 1: Symptoms only n=65 (28 disability pension) Type 2B: Symptoms + intellectual impairment n=46 (24 disability pension)	Type 1 53($\bar{x}$) Type 2 56($\bar{x}$)	Type 1 23($\bar{x}$) Type 2 26($\bar{x}$)	Type 1 6.8($\bar{x}$) years Type 2 6.7($\bar{x}$) years	Structured interview "TUFF" test battery (Swedish-computer administered)	12 subjects improved Type 2B→Type 1 3 subjects deteriorated Type 1→Type 2B Of those remaining the same, the number of symptoms and test performance remained stable except for deterioration in one test (Type 2B group) No indication of progressive disease on removal from exposure

Principle Author (Year)	Characteristics of patients	Age (years)	Period of exposure (years)	Time to follow-up	Measures	Principle Findings
Bowler (1992)	n=56 (female) n= 7 (male) Former microelectronics workers awarded out-of-court settlements for industrial injury at time of original evaluation.	Patients 46.9($\bar{x}$) referents 45.5($\bar{x}$)	6.8($\bar{x}$)	2 years	MMP1	No significant difference between original and follow-up scores for 10 of 13 scales. 3 scales showed higher scores at follow-up (defensiveness, depression, generalised anxiety) All scores clinically elevated
Lindgren (1997)	14 cases of CTE (male). Type 2B participants in rehabilitation programme (10 weeks)	33-60 (median 50)	13-38 (median 24)	Assessment pre-intervention x 2. Post-intervention at 6 months follow-up.	SCL-90 Social Interaction Schedule CPRS/CNRS WHO/NCTB	Some reduction in symptoms and improvement in performance on 2 tests, 1 sustained at 6 months
Abjornsson (1998)	Diagnosis of solvent-induced toxic encepholopathy n=13 treated with psychological intervention (9 had disability pension) n=26 untreated (8 had disability pension) unexposed referents n=39 All male	treated group 57($\bar{x}$) untreated group 54($\bar{x}$) referents 53($\bar{x}$)	NS	13 years	SCL-90 Sense of coherence scale Social Interaction Schedule Strategies to handle stress (4 tests)	No change in test performance of treated or untreated group. Both groups improved in terms of social functioning but remained impaired relative to referents
Dryson (2000)	21 cases of solvent-induced CTE	25-53 (range)	NS Exposure score (duration x occupation x level)	6-42 months 27 months ($\bar{x}$)	Symptoms Cognitive tests (not specified)	7 subjects improved scores on tests, 5 showed fewer symptoms. 3 subjects improved on both measures Those most impaired at first assessment showed significantly more improvement RR 3.86 No association between exposure score or severity of diagnosis and extent of recovery

Table VII

Case-Referent (CR) and Cohort (C) Studies

Principle Author (Year)	Study Design	Cases/Cohort	Referents/Cohort	Principle Findings	Comments
Axelson (1976)	CR	n=151 disability pension for mental disorder (construction industry) 1969-1973	n=248 disability pension for non-mental disorder (construction industry) 1969-1973	Significant overall RR 1.8 for non-specific neuropsychiatric disorders in solvent exposed ≤ 30 years exposure RR 1.3 > 30 years exposure RR 2.1	Psychotic disease and dementia due to head injury excluded alcoholism included exposure = years working as painter, varnisher or carpet layer With alcohol excluded ≤ 30 years exposure RR 1.1 > 30 years exposure RR 2.3
Mikkelsen (1980)	C	n=2601 painters 1971-1975	(1) n=1790 bricklayers 1971-1975 (2) all Copenhagen males >30 years old	RR of disability pension due to "pre-senile dementia" of 3.5 in painters For dementia with cause indication RR 2.0 No increased risk for other psychiatric disease	"Diagnosis" of "dementia" in Denmark is different (less severe condition) than in UK Diagnosis may have been more likely in painters group (physician knowledge of effects)
Olsen (1980)	CR	n=141 disability pension for psychiatric disorder (cabinet makers and carpenters) 1971-1975	n=146 disability pension for non-psychiatric disorder (cabinet makers and carpenters) 1971-1975	High solvent exposure (> 4,000 hours) significantly associated with risk of: (1) psychiatric diagnosis RR 2.80 (2) dementia RR 2.00 (3) neurosis RR 3.11	Occupational exposure history from questionnaires Response rate approximately 90%
Heyman (1984)	CR	n=40 diagnosed with Alzheimer's participants in previous study	n=80 community controls	No significant association between Alzheimer's and solvent exposure	Referents matched for age, sex and race

Principle Author (Year)	Study Design	Cases/Cohort	Referents/Cohort	Principle Findings	Comments
Lindstrom (1984)	CR	n=374 disability pension for psychiatric disorder (construction industry) 1978-1980	n=374 disability pension for non-psychiatric disorder (construction industry) 1978-1980	Significant OR 5.5 for neurosis, personality disorders and psychosomatic disease in solvent exposed Non-significant for all neuropsychiatric diagnoses together	Cases and referents matched for age and time of pension Solvent exposure from job title Association with neuroses but not alcoholism or dementia
French (1985)	CR	n=78 patients diagnosed with Alzheimer's 1979-1982	n=78 neighbourhood controls. No Alzheimer's	No significant association between Alzheimer's and solvent exposure	Cases and referents age, race and sex matched
Rasmussen (1985)	CR	n=207 males admitted to geriatric ward with neuropsychiatric diagnosis	n=110 males admitted to geriatric ward with other diagnosis	Slightly elevated but non-significant risk of psychiatric disease and dementia in those with previous solvent exposure	Solvent exposure assessed by telephone interviews and questionnaires
O'Flynn (1987)	CR	n=557 deaths due to pre-senile dementia age < 65 1970-1979	n=557 deaths due to other causes age < 65 1970-1979	No significant association between Alzheimer's and solvent exposure RR 1.14 (probable + possible exposure)	Cases and referents age matched Solvent exposure graded according to last job title (none, possible, probable)
van Vliet (1987)	CR	n=98 disability pension for psychiatric disorder (painters) (time not stated)	n=141 disability pension for psychiatric disorder (construction workers) (time not stated)	No indication of more cases of typical symptom complex associated with CTE in painters	Data taken from medical files – some incomplete No cases of "dementia" in painters – but different criteria in different countries
Shalat (1988)	CR	n=98 patients with Alzheimer's at one hospital 1975-1985	n=162 community controls selected from voters register	No significant association between Alzheimer's and solvent exposure	Cases and referents matched for age, sex and geographical area

Principle Author (Year)	Study Design	Cases/Cohort	Referents/Cohort	Principle Findings	Comments
Gubéran (1989)	C	n=1,916 painters defined by 1970 Geneva census 1970-1984	n=1,948 electricians defined by 1970 Geneva census 1970-1984	No increased risk for neuropsychiatric disability in painters if alcoholism excluded With alcoholism RR 10.9 Significant increased risk for somatic conditions in painters RR 1.6	Painters significantly increased risk of dying from alcoholism SMR 625 and from cirrhosis SMR 159
Brackbill (1990)	CR	n=3,565 disability pension for psychiatric condition (US Social Security 20% sample) 1969-1973 1975-1976	n=83,245 disability pension for non-psychiatric condition (US Social Security 20% sample) 1969-1973 1975-1976	Significant association with neuropsychiatric disability for: All painters OR 1.42 Construction painters OR 1.47 None in spray painters OR for dementia non-significant	OR adjusted for age, education and time period Authors note, distribution of various diseases different in USA from Scandinavia so classification may be different Exposure classified by job title only
Riise (1990)	CR	n=199 mates and captains awarded disability pension 1970-1986 from cohort of Norwegian seamen (n=1687)	n=4 x 199 mates and seamen not awarded disability pension 1970-1986	Higher risk of disability pension if: (1) worked on oil tankers OR 5.84 (2) mate OR 4.84 Higher risk of psychiatric diagnosis if: (1) mate OR 5.11 (2) longer employment ≤ 5 years OR 5.59 > 5 years OR 8.40	Results may have been influenced by other factors which increase risk of neuropsychiatric disease in tanker crews

Principle Author (Year)	Study Design	Cases/Cohort	Referents/Cohort	Principle Findings	Comments
van Vliet (1990) (also reported in AJIM 1990)	CR	n=252 disability pension for psychiatric disorder (painters and construction workers) 1984-1986	n=822 random sample from painters and construction workers union	Exposure to solvents significantly associated with risk of specifically neurotic disorder OR 2.3	Occupational history from questionnaires Low response rate (approximately 50%) Classification of neuropsychiatric disease made by physicians (not psychiatrists)
Cherry (1992)	CR	n=309 patients admitted to 18 psychiatric hospitals 1978-1985 diagnosis of organic dementia, psycho-organic syndrome, cerebral atrophy	n=309 patients admitted to 18 psychiatric hospitals 1978-1985 other diagnosis + patients admitted to general hospital	Significant OR for solvent exposure among cases compared referents (1.4) No excess risk if alcohol-related diagnosis excluded	Reliability of exposure assessment checked using three methods Patients all first admission (male)
Labrèche (1992)	CR	n=381 patients admitted to two psychiatric hospitals with psychiatric diagnosis 1981-1985	n=381 patients admitted to two general hospitals with non-psychiatric diagnosis 1981-1985	No increased risk of psychiatric admission in patients exposed to moderate or high levels of solvents for at least 10 years	Reliability of exposure assessment checked using three methods Included all male admissions age 40-69 admitted for ≥ 5 days for first time
Lundberg (1992)	C	n=767 painters born after 1925 members of union in 1965 1971-1984	n=1,212 carpenters born after 1925 members of union in 1965 1971-1984	For painters (1) significant excess risk RR 8.0 of early retirement (mainly alcoholism) (2) significant excess risk of psychiatric care RR 1.5 (mainly alcoholism) (3) no excess risk of alcohol-related crime (4) no excess risk of alcohol-related disease or violent death	Also excess risk of alcoholism among painters RR 1.7, comparing painters n=36 and carpenters n=34 who were registered due to alcoholism in at least two registers or registered for alcohol crime at least twice (i.e. judged to have more severe problems)

Principle Author (Year)	Study Design	Cases/Cohort	Referents/Cohort	Principle Findings	Comments
Nelson (1994)	CR	n=299 disability retirement for neurological disease (worked in 1 of 8 car factories) 1980-1988	(1) n=326 disability retirement for non-neurological disease worked in 1 of 8 car factories 1980-1988 (2) n=530 currently working in 1 of 8 car factories	No association between solvent exposure and neurological disease (cases had less exposure than referents)	Participants had to have worked ≥ 10 years to gain disability retirement – may have selected out most affected Some association observed between exposure and multiple sclerosis, but numbers small and risk non-significant
Kukull (1995)	CR	n=193 patients entering health maintenance organisation 1987-1992 diagnosis of Alzheimer's 1987-1992	n=243 patients entering health maintenance organisation 1987-1992 no neurological disease 1987-1992	History of solvent exposure gave OR for Alzheimer's of 2.3 whole group and 6.0 males only	Patient group represented 66% of all patients (34% declined to take part) OR adjusted for age and sex Information on solvent exposures given by proxy respondents for casers and referents