

Occupational Safety and Health Information Series

Chronic Organic Solvent Neurotoxicity: Diagnostic Criteria

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Introduction

Organic solvents are volatile compounds or mixtures that are relatively stable chemically and that exist in the liquid state at temperatures of approximately 0 - 250 degrees C. They are widely used in industry in paints, adhesives, glues, coatings and degreasing/cleaning agents, and in the production of dyes, polymers, plastics, textiles, printing inks, agricultural products and pharmaceuticals. Based on US data, approximately 100,000 New Zealand workers are potentially exposed to organic solvents.¹ Although acute effects (CNS depression, psychomotor impairment, and narcosis) are well recognised, chronic effects have also been observed in conjunction with long term exposure. Several studies have shown that long-term exposure may impair functions of the central nervous system such as memory, concentration, and perceptual and psychomotor speed and accuracy, and that some of these effects persist even when exposure has ceased.²

Solvent neurotoxicity has been classified by the 1985 International Solvent Workshop³ as follows:

Type 1: (the least severe)

Characterised by fatigue, memory impairment, irritability, difficulty in concentrating, and mild mood disturbance. This corresponds to the WHO classification of organic affective syndrome.⁴ It is reversible on removal from exposure.

Type 2:

Symptoms of neurotoxicity and abnormalities of performance on neuropsychological testing. Type 2 disorder has been subdivided into:

Type 2A: sustained personality or mood change, and

Type 2B: impairment in intellectual function.

This level corresponds to the WHO classification of mild chronic toxic encephalopathy. New Zealand research^{5,6} and clinical experience suggests that the majority of workers diagnosed as Type 2 have symptoms from both Types 2A and 2B. It is therefore recommended that these two subtypes be collapsed and called Type 2.

Type 3: (most severe)

Global deterioration in intellectual and memory functions (dementia). This corresponds to the WHO classification of severe chronic toxic encephalopathy and is usually irreversible.

It is the Type 1 and 2 disorders which are most likely among solvent-exposed workers.¹

Disease Criteria

Criteria for the diagnosis of solvent intoxication have been established in several countries. For New Zealand, the following criteria are recommended, based on those of Finland and Sweden:⁷

Long and/or intense exposure to solvents

Relevant symptoms

Presence of pathological findings in terms of an objective measure such as neuropsychological tests

Other organic or psychiatric diseases reasonably well excluded

For the purposes of deciding whether a case meets these criteria or not, the guidelines which follow should be used.

Long and/or Intense Exposure to Solvents

- Unless exposure has been unduly intense, it will in general be expected that duration of exposure will exceed 10 years.²
- Although prolonged low-level exposure may give rise to symptoms, it will in general be expected that exposure levels will have been at or around the appropriate New Zealand Workplace Exposure Standard⁸ for the solvent or solvents in question.
- Not all solvents are equally neurotoxic. Commonly used solvents which are, or are suspected of being, neurotoxic are:
 - trichloroethylene
 - styrene
 - tetrachloroethane
 - xylene
 - white spirit
 - methylene chloride and
 - voluntary abused toluene.⁹
- Carbon disulphide, although long recognised as neurotoxic, is used only in limited areas in New Zealand, such as in the manufacture of pharmaceuticals and in some laboratory procedures.
- Methyl n-butyl ketone and n-hexane are recognised causes of peripheral neuropathy. Although not used *per se*, both can be found in small amounts in other mixtures. N-hexane in particular is found as a component of general solvents such as white spirits, which contain low boiling point range hydrocarbons. It would usually constitute less than 15%. Methyl n-butyl ketone may be found as a contaminant in other ketones.

Relevant Symptoms

Symptoms consistent with chronic solvent neurotoxicity include:

- fatigue
- sleep disturbances
- irritability
- anxiety
- loss of appetite
- alcohol intolerance
- memory and concentration difficulties.^{2,5,6}

There is often impairment of frontal lobe function, resulting in problems with planning, organisation and abstract thinking.^{5,6,10,11}

Presence of Pathological Findings in terms of an Objective Measure

Objective measures may include one or more of the following:

- **Clinical Neurological Examination**

Clinical examination of the nervous system may show signs of sensory or sensorimotor polyneuropathy. In general however, findings on clinical neurological examination show poor correlation with exposure to solvents.¹² Increased postural sway has been reported in solvent exposed subjects.¹³

- **Neurophysiological Tests**

Nerve Conduction Studies

Reduction in sensory and motor nerve conduction velocities has been shown to be related to solvent exposure.¹⁴ Prolongation of distal latency, and lowering of amplitudes in sensory and motor nerves, may also be found.¹⁵

Electroencephalography

Increased slow activity has been detected in the EEG of workers with solvent poisoning.¹⁴ Statistically significant EEG changes have been found in solvent exposed populations compared with reference populations.¹ Studies with computer enhanced electroencephalography suggest that distinctive patterns may be seen in some conditions, such as alcoholism, and perhaps in solvent toxicity.¹⁶

Evoked Potentials

These measure brain or nerve activity evoked by a visual, auditory or somatosensory stimulus. Delays in the latencies of evoked potentials can be seen in neurotoxic lesions of the sensory tracts to the brain. Diminished amplitude and changes in the shape of the peaks of the evoked potentials also occur.¹⁴

Electroneuromyography

This provides information about peripheral nerves, the neuromuscular junction, and muscles. Neurogenic abnormalities may be seen in solvent poisoning.¹⁴

Visual Contrast Sensitivity

Statistically significant abnormalities in contrast sensitivity have been reported in workforces exposed to solvents and in a case series of solvent induced encephalopathy.¹⁷

- **Neuroimaging**

Computerised Tomography (CT)

This may be used to show structural changes associated with severe neurotoxicity, such as widening of the sulci and dilation of the ventricles. It is, however, not sensitive to early effects, as pertains to most industrial exposure. It is useful, however, in excluding other pathology.

Magnetic Resonance Imaging (MRI)

Although MRI is highly sensitive to structural damage it has the same limitations as CT.

Positron Emission Tomography (PET)

PET measures regional blood flow, substrate metabolism, neurotransmitter and neuroreceptor activity.¹⁸ It has been used to show patterns of brain lesions thought to be typical of neurotoxicity, despite differences in toxin structure, and correlates well with clinical and neuropsychological testing.¹⁹

PET is not available in New Zealand.

Ceretec Scanning

Ceretec scanning measures cerebral blood flow by means of a short-lived isotope of technetium, and a rotating gamma camera. Ceretec scanning may be useful in solvent neurotoxicity.

- **Neuropsychological Testing**

This has shown statistically significant differences between solvent-exposed and reference groups in such CNS functions as simple reaction time, manual dexterity, perceptual speed and new learning.¹ Standardised batteries of tests, such as the WHO Battery²⁰ and the Swedish TUFF Battery²¹ have been developed, both for screening purposes, and for assessment of individuals.

Neuropsychological performance testing has been the main method of assessing chronic solvent effects on exposed workers.^{5,6}

Other Organic or Psychiatric Disease Reasonably Well Excluded

(not attributable to solvent neurotoxicity or its psychosocial consequences).

This may involve imaging such as CT scanning, or a psychiatric examination, depending on the symptomatology.

Clinical Assessment

Screening Questionnaire

Where chronic effects are suspected, either in an individual, or in groups of exposed workers, a screening symptom questionnaire can be used. The recommended screening tool is the Swedish *Questionnaire 16*.²² (Appendix 1)

Further investigation is indicated if, on completion of *Questionnaire 16*, there is:

A total of **more than 4 positive answers** in a worker **younger than 28 years** of age, or

A total of **more than 6 positive answers** in a worker aged **28 years or older**.

Answers to the questions are entirely subjective, and subject to bias, but a positive response to the control question (number 16) throws some doubt on the validity of the answers to the previous questions.

Questionnaire 16 only contains questions relevant for the monitoring of neuropsychiatric symptoms, and cannot be used for acute effects of solvents, or effects on other body systems.

Clinical Examination

A full neurological examination is recommended. Any reduction in sense of light touch or pain, increase in vibration threshold, impaired balance or increased postural sway should be recorded. Such findings are often slight and cannot be considered diagnostic, but will add to the weight of evidence when evaluating a case.

Neuropsychological Testing

Workers who reach the criteria for exposure, and show positive cognitive and/or psychosocial effects of exposure on clinical interview, should undergo a neuropsychological assessment, which will provide stronger evidence for or against long-term cognitive and psychosocial defects. This assessment should be performed by a qualified clinical neuropsychologist, and would ideally take place following a significant period away from the solvents to ensure that any deficits found are not acute and transient.

A suggested assessment format would include the following tests (see page 9) or alternative tests that assess similar functions at a similar level. This is considered a minimal battery and there may be many additional tests that would add information about the level and type of deficits and spared functions. A more extensive battery may be necessary in some difficult cases to assess possible neurotoxicity, and also to guide rehabilitation.

Surveillance Criteria

Surveillance of solvent-exposed workers will require attention to all of the following factors:

Environmental Measurements

Standards for air levels of solvents in workplaces are contained in the OSH publication *Workplace Exposure Standards*.⁸

The solvent/s concerned should be identified and measured where practicable. Levels exceeding the Workplace Exposure Standard (WES) should be reduced by appropriate engineering controls.

Biological Exposure Indices

Uptake and excretion of solvents by the body can be determined by measuring the solvent itself, or a metabolite in the blood, urine or expired air of the worker concerned. In practice, urinary levels are the most common form of measurement. Examples of urinary metabolites used for biological measurements are:

SOLVENT	METABOLITE
styrene	mandelic acid
toluene	hippuric acid
xylene	methylhippuric acid
trichloroethylene	trichloroethanol and trichloroacetic acid
1,1,1-trichloroethane	trichloroethanol and trichloroacetic acid

***Note:** Both environmental and biological measurements will reflect current exposure. In cases of suspected chronic effects of solvents, an attempt should be made at assessing long-term exposure by means of previous environmental measurements, if available, or by an estimate based on work history.*

Standards for urinary levels are contained in the OSH publication *Workplace Exposure Standards*.⁸

Neuropsychological Assessment Format

Initial Interview

The initial interview, which would typically take about thirty minutes, is carried out, preferably with a close relative also present, to assess psychosocial functioning, coping abilities and other factors that may cause similar symptoms, or exacerbate symptoms (e.g. a minor closed head injury, alcohol and drug intake, psychosocial stress levels), and to assess the effects of memory impairment and other cognitive problems in day-to-day life.

Formal education, hobbies and other activities the person is involved in or has been involved in previously will assist in an accurate assessment of premorbid IQ estimate.

Formal Neuropsychological Testing

All the tests suggested here can be carried out without the aid of a computer. However, for some functions (e.g. vigilance) there are other tests that may be better but that require a computer for the presentation of stimuli and scoring.

For descriptions of these tests see Lezak²³ and Spreen and Strauss.²⁴

The pattern of test results would vary to some extent across individuals as a result of premorbid abilities, the presence and extent of organic damage or dysfunction, and even possible location of organic damage. However, most research suggests damage is quite diffuse and results primarily in impairments of arousal, concentration, vigilance and response speed.^{5,6,8,11,25}

In cases where damage is more severe, verbal and nonverbal memory and visuospatial abilities may be affected. In addition, deficits usually seen after frontal-lobe damage are also sometimes found (e.g. impaired abstract thinking, organisation and planning abilities).^{8,10,11,25} Frontal lobe deficits can be particularly debilitating, and are often strongly supported by the problems the individual is experiencing in day-to-day life; e.g. poor ability to plan ahead, emotional lability (usually depression), excessive fatigue, lowered tolerance to alcohol, hypersensitivity to noise. Generally the NART, Vocabulary and Picture Completion tests and Digits Forward would not be impaired, and act as good indicators of premorbid ability. Any of the other tests may show impairment.

The importance of the interpretation of the overall pattern of results, including the psychosocial data gathered from the initial interview, cannot be stressed enough. This is why it is important that an experienced and qualified clinical neuropsychologist carries out the assessment of long-term cognitive deficit.

The entire battery, including the thirty-minute initial interview, would take about two hours to administer, although it may take much longer with individuals who are very slow, or who are very upset and take longer to relax so that they are able to do their best on the tests.

Scoring and interpretation of the tests and the writing of a brief report to a semi-standardised format (this would not include rehabilitation suggestions but

simply a profile of the individual’s deficits and strengths and the interpretation of these in the light of the interview data), would take a further one and a half to two hours.

For individuals where significant impairment is found, further exposure should be avoided, and an assessment is recommended in nine to twelve months’ time, to assess recovery.

FORMAL NEUROPSYCHOLOGICAL TESTING			
Suggested Test		Main Function Tested	Approx. Testing Time
1	New Adult Reading Test (NART) and “Vocabulary” from WAIS-R	Estimate of the premorbid IQ	Minutes 10
2	Cancellation Test	Vigilance	5
3	“Digit Symbol” from WAIS-R	Psychomotor speed	5
4	Picture Completion” from WAIS-R	Simple visuospatial perception	5
5	“Block Design” from WAIS-R	Complex visuospatial perception and speed	5
6	Rey-Osterreith Complex Figure Test - with 30-45 minute delayed recall	Complex visuospatial perception and motor co-ordination, planning ahead, and long-term visuospatial memory	10
7	Digit Span	Immediate memory and mental tracking	10
8	Selective Reminding Test (12 unrelated words over 12 trials) - including a recognition trial <u>or</u> California Verbal Learning Test.	Long-term verbal memory	10
9	(a) “Similarities” from WAIS-R (b) Wisconsin Card Sorting (c) Also copy of a Complex Figure (d) Oral Word Fluency	Frontal lobe abilities (abstract thinking, organisation and planning, changing set, word initiation)	20

Treatment Guidelines

Management of a confirmed case of solvent neurotoxicity should follow these steps:

1 Remove from further exposure to solvents

This may be possible within the employing company. In some cases relocation to another job in the factory is possible. In other cases it will be necessary to change employment.

2 Retrain for another job where possible

Workers with significant impairment will find it hard to both find and cope with a different job. Retirement on medical grounds may be the only option.

3 Psychological interventions

These may take the form of teaching anxiety/stress management, anger management, coping skills (including ways of coping with a memory impairment), and the provision of information about their problems and their causes.

Facilitating the understanding and support of family and friends is also important.¹⁰

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QUESTIONNAIRE 16*A Questionnaire for CNS Symptoms*

No.	Questions	Yes	No
1	Do you have a short memory?	<input type="checkbox"/>	<input type="checkbox"/>
2	Have your relatives told you that you have a short memory?	<input type="checkbox"/>	<input type="checkbox"/>
3	Do you often make notes about what you must remember?	<input type="checkbox"/>	<input type="checkbox"/>
4	Do you often have to go back and check things you have done such as turned off the stove, locked the door, etc?	<input type="checkbox"/>	<input type="checkbox"/>
5	Do you generally find it hard to get the meaning from reading newspapers and books?	<input type="checkbox"/>	<input type="checkbox"/>
6	Do you often have problems with concentrating?	<input type="checkbox"/>	<input type="checkbox"/>
7	Do you often feel irritated without any particular reason?	<input type="checkbox"/>	<input type="checkbox"/>
8	Do you often feel depressed without any particular reason?	<input type="checkbox"/>	<input type="checkbox"/>
9	Are you abnormally tired?	<input type="checkbox"/>	<input type="checkbox"/>
10	Are you less interested in sex than what you think is normal?	<input type="checkbox"/>	<input type="checkbox"/>
11	Do you have palpitations of the heart even when you don't exert yourself?	<input type="checkbox"/>	<input type="checkbox"/>
12	Do you sometimes feel oppression in your chest?	<input type="checkbox"/>	<input type="checkbox"/>
13	Do you perspire without any particular reason?	<input type="checkbox"/>	<input type="checkbox"/>
14	Do you have a headache at least once a week?	<input type="checkbox"/>	<input type="checkbox"/>
15	Do you often have painful tingling in some parts of your body?	<input type="checkbox"/>	<input type="checkbox"/>
16	Do you have any problems with buttoning and unbuttoning?	<input type="checkbox"/>	<input type="checkbox"/>