

## Neurophysiological aspects of the toxicity of organic solvents

by Anna Maria Seppäläinen, MD<sup>1</sup>

SEPPÄLÄINEN AM. Neurophysiological aspects of the toxicity of organic solvents. *Scand J Work Environ Health* 11 (1985): suppl 1, 61–64. Symptoms after long-term exposure to organic solvents are nonspecific, and for both medical and insurance purposes objective demonstration of toxic damage would be desirable at the earliest possible stage of beginning disease. Axonopathy does not dramatically decrease nerve conduction velocities; however, epidemiologic studies may reveal slower conduction velocities, especially in the distal nerve segments, among workers exposed to organic solvents. Among patients with solvent poisoning abnormally slow nerve conduction velocities are detected. Electromyography reveals denervation activity in early axonopathy; loss of motor units is detectable at a later stage. Hexacarbons, eg, n-hexane, have caused changes in visual evoked potentials, namely, prolonged latencies and decreased amplitudes, probably due to axonal lesions within the central nervous system. Electroencephalography (EEG) has been applied in studies of individual patients or patient groups and in epidemiologic approaches. Among patients actual abnormalities, mainly diffuse or local slow wave abnormalities, are frequent. In epidemiologic studies the frequency of abnormal EEG findings is related to overall exposure levels in the studied populations.

*Key terms:* electroencephalography, electromyography, evoked potentials, nerve conduction velocities.

Various solvents and, especially, solvent mixtures are widely used in industry for many purposes. Glues, paints, and degreasing agents are the most usual sources of solvent vapors in the workroom air, although in the production of reinforced plastics monomers (eg, styrene) can also be regarded as organic solvents. Inhalation is the main route of exposure; some exposure can occur through intact skin. The systemic spread and metabolic transformation of the chemical are the prerequisites of neurotoxic effects.

Workers exposed to solvents complain of a variety of symptoms, eg, headache, loss of memory, a drunken feeling, vertigo, tiredness, paresthesiae, numbness, muscle weakness, and others. At the group level many of these symptoms can be connected to solvent exposure, but with individual patients an occupational etiology of these often vague symptoms can be hard to ascertain. However, if damage has actually occurred within the nervous system, it should be detected at an early stage. Actions should then be taken to prevent further damage to the nervous system, which recovers slowly and at times incompletely. There are no curative measures, but the termination of exposure helps nature cure early lesions.

The question can be asked of whether there are objective methods of detecting early damage or dysfunction within the nervous system. Careful neurological examination gives valuable information on disturbed functions, and the quantitative testing of

various sensory modalities adds to the objectivity and sensitivity of testing the cutaneous senses. An overall evaluation of the patient and complete differential diagnostics are also necessary for the actual diagnosis of an occupational disease like solvent poisoning. Neurophysiological methods are valuable indicators that provide objective data on nervous system malfunctions and show the site or sites of lesions. One must not forget that evidence of relevant exposure to solvents is a prerequisite of solvent poisoning. Low-level, occasional occupational exposure is hardly likely to cause damage, but some evidence suggests that long-term exposure to concentrations presently allowable or repeated exposure to high peak concentrations may cause lesions in the nervous system.

The neurophysiological methods used in occupational medicine (7) include electroencephalography (EEG) for examining the central nervous system (12) and electroneuromyography (ENMG) (2) for studying the electrical activity of the nerves and muscles and providing information about peripheral nerves, neuromuscular junction, and muscles. Both methods are based on wide clinical experience with diseases and injuries of the nervous system.

A newer neurophysiological method is the study of evoked potentials (4), ie, the electrical brain (or nerve) activity evoked by an external stimulus, which can be visual, auditory, or somatosensory. A laboratory computer is required to study evoked potentials, since they are so small in amplitude and so buried in basic brain activity that the signal-to-noise ratio has to be improved with an averaging technique. Specific compact systems to study evoked potentials are available commercially, and several electromyographs are also provided with averaging possibilities. Evoked potentials give information about brain activity and

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sensory tracts from the site stimulated to the brain cortex. Neurotoxic lesions are more likely situated in the long sensory tracts than in the cortex, and delays can be expected in the latencies of evoked potentials. Partial lesions in the tracts could also cause diminished amplitude and changes in the shape of the peaks of the evoked potentials. Although the method has attractive possibilities, evoked potentials have rarely been applied in epidemiologic studies of solvent-exposed workers (6).

The best known effects of solvents on the nervous system are neuropathic signs after exposure to hexa-carbons (25). *n*-Hexane and methyl *n*-butyl ketone have caused central peripheral distal axonopathy, ie, a toxic lesion formed by the accumulation of 10-nm neurofilaments close to the terminal portion of axons. Patients complain of numbness, paresthesiae, and diminished strength in distal muscles (3, 5, 10, 11). Sensory conduction velocity is diminished, particularly in distal branches, and the amplitude of the sensory action potential is also diminished. Motor conduction velocity may be reduced, especially in long axons, ie, in leg nerves such as the peroneal and tibial nerves. In these patients electromyography reveals degeneration activity (eg, fibrillations and positive sharp waves), and the number of acting motor units may be reduced. Some of the remaining motor unit potentials show neurogenic changes (eg, increased duration). Similar findings have been published on neuropathy occurring among workers occupationally exposed to carbon disulfide (13, 24).

The neurotoxic effects of *n*-hexane are not limited to the peripheral nervous system. Axons undergo

similar changes also within the central nervous system as has been demonstrated in poisoned cats (14). At the Institute of Occupational Health in Helsinki we could demonstrate increased latencies and reduced amplitudes of various peaks in the visual evoked potentials of workers occupationally exposed (either about twice a week for a few minutes to 30 min or daily for brief periods) to high (2 000–3 000 ppm) peak concentrations of *n*-hexane (22). Persons with abnormalities in their ENMG usually also had low-amplitude visual evoked potentials (VEP), whereas EEG abnormalities per se were less frequent (23).

In epidemiologic studies conducted among groups of workers exposed to solvent mixtures (car painters, industrial spray painters) some individuals have been detected who have shown abnormally slow conduction velocities in one or more nerves, or the average motor conduction velocity of the exposed group has been statistically significantly slower than that of the reference group (16). Swedish and Finnish studies in which the time-weighted average exposure level was about 30 % of the hygienic standard detected similar findings (6, 19). The frequency of abnormally slow nerves among patients with solvent poisoning increased as the exposure levels rose (21).

A follow-up study on patients with solvent poisoning (17) revealed that, at the time of diagnosis, a very high proportion of the patients had neuropathic signs (slowed nerve conduction velocities and/or neurogenic abnormalities in their electromyography) and that these types of abnormalities were permanent (figure 1). Actually, a higher proportion of the patients showed some neuropathic signs six years later, even though the occupational solvent exposure of most of the patients had ceased after or within one to two years of the diagnosis. Some improvement of the ENMG findings was noted for 43 % of the patients, whereas deterioration was found for 33 %. Usually the deterioration was only mild. All these patients had been exposed to various solvent mixtures; 21 of the 87 patients had been exposed solely to tri- or perchloroethylene. Thirteen of these patients had been exposed to both chlorinated hydrocarbons and various solvent mixtures, often simultaneously. The frequency and type of neuropathy was similar among the groups exposed to either solvent mixtures or chlorinated hydrocarbons, whereas neuropathy was slightly more common among the 13 patients exposed to both mixtures and chlorinated hydrocarbons. The neuropathy of these 13 patients was more often both proximal and distal in distribution, and all 13 showed motor neuropathy, while among other patient groups only sensory neuropathy was occasionally demonstrated. Probably there had been some interaction between the different solvents, or perhaps the solvent mixtures had potentiated the effect of chlorinated hydrocarbons similar to the manner in which methyl ethyl ketone potentiates the neurotoxic effects of *n*-hexane (1). The toxic interactions that arise after

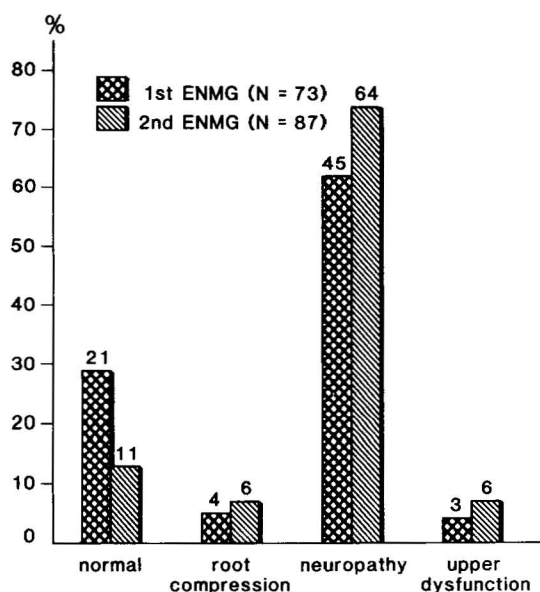


**Figure 1.** Types of electroneuromyographic (ENMG) findings in the initial examination and in the reexamination of patients with solvent poisoning. The numerals at the top of the columns are the numbers of cases [reprinted from Seppäläinen & Antti-Poika (17)].

mixed exposure are poorly known, but they may play an important role in producing clinical symptoms and signs.

Toxic encephalopathy after solvent exposure is a more controversial issue than toxic polyneuropathy. Many of the symptoms that have been associated with solvent exposure seem to refer to the central nervous system. Groups of solvent-exposed workers have had poorer performances on certain psychological tests when compared with unexposed groups (6, 8). Great problems are encountered in the assessment of central nervous system functions. There is wide interindividual variation in the basic capacities and in the capacity to compensate for loss. Furthermore, the plasticity of the nervous system is great, especially at young ages. If it were feasible, it would be useful to measure, not only the actual capacity, but also the remaining plasticity. At present one must be satisfied with assessments of loss.

EEG reveals a rather acute loss of neurons or loss of neuronal functions. Such loss is indicated as increased low-frequency activity in the damaged region. In such a case the normal rhythmic 8- to 13-cycle/s alpha activity is disturbed, and instead one sees irregular or rhythmic theta (4–7 cycles/s) or delta (0.5–3 cycles/s) activity. Such phenomena can be demonstrated in acute severe poisoning, but with time the EEG activity tends to return to its normal features. No quick changes in the EEG can be expected when encephalopathy develops slowly during long-term solvent exposure. However, increased slow activity is detected in the EEG of patients with solvent poisoning or workers with various symptoms (21). With somewhat higher exposure levels, we could detect a high proportion of abnormal EEG findings among solvent-exposed workers who, around 1970, came to the Institute of Occupational Health, Helsinki, for periodic examinations and who complained of some central nervous symptoms (15). When their exposure was evaluated independently of the EEG results, it was noted that the prevalence of abnormal EEG findings was much higher among workers exposed to levels close to the hygienic standard. The EEG abnormalities were mainly slow wave abnormalities, diffuse slow wave abnormalities being the most frequent. However, 5 % of the exposed persons showed paroxysmal EEG abnormalities, which are usually found in epileptic disorders. Actual convulsions are rarely associated with solvent exposure, but solvents may lower the threshold for convulsions, as does alcohol. In present industrial settings, at least in the Scandinavian countries, EEG abnormalities are not frequent among solvent-exposed groups, but slightly increased frequencies can be expected in light of epidemiologic findings (table 1). House painters' solvent exposure is generally low, and the frequency of EEG abnormalities among painters has been found to be within normal variations (20), whereas car painters in Finland have been shown to have ab-

normal EEG findings more often (19). EEG abnormalities are often found among patients with solvent poisoning, and the EEG abnormalities of half of a group of such patients still persisted several years after diagnosis (17).

Exposure-response relationships are hard to detect for solvent exposure, as it is impossible to assess individual, long-term exposure reliably in quantitative terms. Peak exposure periods are also very difficult to evaluate. A relatively good measure of individual exposure to styrene is the urinary concentration of mandelic acid. When urinary mandelic acid concentrations were measured on five occasions over five consecutive weeks, the prevalence of abnormal EEG findings was related to the mandelic acid concentrations. Furthermore, the frequency of abnormal EEG findings was clearly higher than among the normal population when the urinary mandelic acid concentration exceeded 700 mg/l (4.9 mmol) (figure 2), which corresponds to a time-weighted-average styrene concentration of 30–40 ppm in the air (9, 18).

**Table 1.** Percentages of abnormal electroencephalograms among solvent-exposed workers in various studies conducted at the Institute of Occupational Health in Helsinki.

| Number of workers*                             | Percentage |
|------------------------------------------------|------------|
| 72 painters in the building industry (20)      | 17         |
| 102 car painters (19)                          | 31         |
| 233 solvent-exposed workers with symptoms (15) | 40–72      |
| 107 patients with solvent poisoning (21)       | 65         |
| 87 patients with solvent poisoning (17)        | 67         |

\* Reference in parentheses.

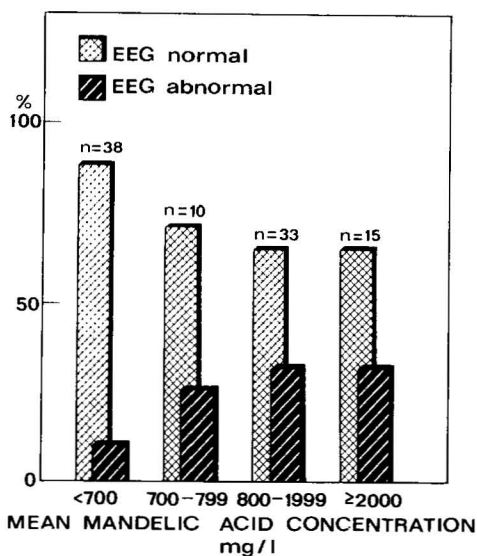


**Figure 2.** Relative frequency of the normal and abnormal electroencephalograms (EEG) of the exposed subjects according to the subjects' urinary mandelic acid concentrations [reprinted from Härkönen et al (9)].

Although EEG studies have been applied in epidemiologic research and for the individual diagnosis of patients with suspected solvent poisoning, they are not suitable for screening purposes, since 10–15 % of normal populations, or even more, may have EEG abnormalities. Wrong positive results are common too. Questionnaires or medical interviews are better for screening. Only subjects with suspected toxic effects should be sent for further examination, which then should include neurophysiological studies. At our Institute solvent-exposed patients are routinely studied with EEG and for visual evoked potentials. ENMG examinations are performed for persons who complain of paresthesiae, numbness, or diminished strength. All the results are evaluated together, and an adequate differential diagnosis is considered. The occupational exposure is checked from the patient and from the employer, and specific hygienic measurements are taken if necessary. Exposure levels have decreased in recent years, and chronic solvent poisoning has thus become rare. Mild effects have been detected in some cases, and hygienic improvements in the work environment have been suggested.

Neurophysiological methods are sensitive but cannot provide an etiologic diagnosis in toxic cases. However, if the same patient has both central and peripheral nervous system findings, toxic etiology is a relevant possibility, since other diseases seldom affect both these systems.

## References

1. Altenkirch H, Mager J, Stoltenburg G, Helmbrecht J. Toxic polyneuropathies after sniffing a glue thinner. *J Neurol* 214 (1977) 137–152.
2. Aminoff MJ. *Electrodiagnosis in clinical neurology*. Churchill Livingstone, New York, NY 1980.
3. Billmaier D, Yee HT, Allen N, Craft B, Williams N, Epstein S, Fontaine R. Peripheral neuropathy in a coated fabrics plant. *J Occup Med* 16 (1974) 665–671.
4. Chiappa KH. *Evoked potentials in clinical medicine*. Raven Press, New York, NY 1983.
5. Cianchetti C, Abbritti G, Perticoni A, Siracusa A, Curradi F. Toxic polyneuropathy of shoe-industry workers: A study of 122 cases. *J Neurol Neurosurg Psychiatry* 39 (1976) 1151–1161.
6. Elofsson SA, Gamberale F, Hindmarsch T, Iregren A, Isaksson A, Johnsson I, Knave B, Lydahl E, Mindus P, Persson HE, Philipson B, Steby M, Struwe G, Söderman E, Wennberg A, Widen L. Exposure to organic solvents: A cross-sectional epidemiologic investigation on occupationally exposed car and industrial spray painters with special reference to the nervous system. *Scand J Work Environ Health* 6 (1980) 239–273.
7. Gilioli R, Cassitto MG, Foà V, ed. *Neurobehavioral methods in occupational health*. Pergamon Press, Oxford 1983.
8. Hänninen H, Eskelinen L, Husman K, Nurminen M. Behavioral effects of long-term exposure to a mixture of organic solvents. *Scand J Work Environ Health* 2 (1976) 240–255.
9. Härkönen H, Lindström K, Seppäläinen AM, Asp S, Hernberg S. Exposure-response relationship between styrene exposure and central nervous functions. *Scand J Work Environ Health* 4 (1978) 53–59.
10. Herskowitz A, Ishii N, Schaumburg H. n-Hexane neuropathy: A syndrome occurring as a result of industrial exposure. *New Engl J Med* 285 (1971) 82–85.
11. Iida M, Yamamura Y, Sobue I. Electromyographic findings and conduction velocity on n-hexane polyneuropathy. *Electromyography* 9 (1969) 247–261.
12. Klass DW, Daly DD, ed. *Current practice of clinical electroencephalography*. Raven Press, New York, NY 1979.
13. Lukás E. Leitungsgeschwindigkeit peripherer Nerven bei Schwefelkohlenstoff ausgesetzten Personen. *Int J Clin Pharmacol* 2 (1969) 354–358.
14. Schaumburg HH, Spencer PS. Environmental hydrocarbons produce degeneration in cat hypothalamus and optic tract. *Science* 199 (1978) 199–200.
15. Seppäläinen AM. Neurotoxic effects of industrial solvents. *Electroencephalogr Clin Neurophysiol* 34 (1973) 702–703.
16. Seppäläinen AM. The use of clinical neurophysiological methods in studies of workers exposed to solvents. In: *Kyoto Symposia (EEG suppl no 36)*. Elsevier, Amsterdam 1982, pp 693–700.
17. Seppäläinen AM, Antti-Poika M. Time course of electrophysiological findings for patients with solvent poisoning: A descriptive study. *Scand J Work Environ Health* 9 (1983) 15–24.
18. Seppäläinen AM, Härkönen H. Neurophysiological findings among workers occupationally exposed to styrene. *Scand J Work Environ Health* 2 (1976) 140–146.
19. Seppäläinen AM, Husman K, Mårtensson C. Neurophysiological effects of long-term exposure to a mixture of organic solvents. *Scand J Work Environ Health* 4 (1978) 304–314.
20. Seppäläinen AM, Lindström K. Neurophysiological findings among house painters exposed to solvents. *Scand J Work Environ Health* 8 (1982): suppl 1, 131–135.
21. Seppäläinen AM, Lindström K, Martelin T. Neurophysiological and psychological picture of solvent poisoning. *Am J Ind Med* 1 (1980) 31–42.
22. Seppäläinen AM, Raitta C, Huuskonen MS. n-Hexane-induced changes in visual evoked potentials and electroretinograms of industrial workers. *Electroenceph Clin Neurophysiol* 47 (1979) 492–498.
23. Seppäläinen AM, Raitta C, Huuskonen MS. Nervous and visual effects of occupational n-hexane exposure. In: *Lechner H, Aranibar A, ed. EEG and clinical neurophysiology*. Excerpta Medica, Amsterdam 1980, pp 656–661.
24. Seppäläinen AM, Tolonen M, Karli P, Hänninen H, Hernberg S. Neurophysiological findings in chronic carbon disulfide poisoning: A descriptive study. *Work Environ Health* 9 (1972) 71–75.
25. Spencer PS, Couri D, Schaumburg HH. n-Hexane and methyl n-butyl ketone. In: *Spencer PS, Schaumburg HH, ed. Experimental and clinical neurotoxicology*. Williams & Wilkins, Baltimore, MD 1980, pp 456–475.