

Overview of the neurotoxic effects in solvent-exposed workers

by

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Abstract

Workers exposed to solvents are at risk to develop a chronic toxic encephalopathy, although effects (promoting or etiological) on other central and peripheral nervous system diseases may be possible. Careful monitoring of exposure (environmental monitoring and bio-monitoring) but also bio-effect monitoring is strictly needed. A review of the literature is given. This text is the summary of the report made for the Fund for Occupational Diseases (Fonds voor de Beroepsziekten), Belgium, 1998.

Keywords

Neurotoxicity syndromes, organic solvents, chronic toxic encephalopathy.

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Introduction

Organic solvents represent a group of aliphatic and aromatic organic compounds which are usually lipophilic and more or less volatile. Historically, some solvents (e.g. trichloroethylene and chloroform) were used in medicine as anesthetics because of their narcotic properties. Propofol (2,6-diisopropylphenol) is still widely used in this respect. However, in industry numerous chemical or technical processes rely on specific properties of organic solvents which may cause substantial exposure to these substances in the work force. Although the acute neurotoxic potentials of most solvents were known for a long time, it was not earlier than the second half of the 20th century that chronic or delayed neurotoxicity due to occupational solvent exposure became a scientific issue. Since then, case-reports, case-control studies, cross-sectional and follow-up investigations documented a variety of exposure conditions (aromatic or aliphatic solvents, or solvent mixtures) which may cause clinical neurological or neurophysiological effects, neuropsychological deficits, influence on neuro-endocrinological function or neuro-radiological changes (1-3). Pre-narcotic symptoms evolving to coma with or without residual neurobehavioral sequels have been described as resulting from acute exposure, while invalidating diseases such as organic encephalopathy (or organic psycho-syndrome, OPS), depression, psychosis, sleep apnoea, multiple sclerosis, dementia, Parkinson's disease, and amyotrophic lateral sclerosis were considered as chronic or delayed effects of long-term solvent exposure (1-4). Minor problems such as dyschromatopsia, loss of hearing and smell, and vestibular dysfunction were also reported in chronic exposure conditions with a variety of solvents (1-3). It appeared thus that exposure to most solvents could induce deterioration of different central nervous system functions as well as peripheral nervous functions. The characterization of the exposure conditions (exposure intensity, exposure duration, type of solvent), however, was mostly insufficient and therefore frequently led to controversy or confusion. This review attempts to give an overview of what is known about the neurotoxic effects of occupational solvent exposure in humans and the implications of this knowledge to early detection and prevention.

Central Nervous System Effects

Organic psycho-syndrome due to solvent exposure

Acute effects

In most cases there is no discussion about the etiology of this disease when the time-lag between the intoxication and the clinical symptoms is

not more than a few hours (5). In cases of acute or subacute intoxication with organic solvents, symptoms of eye and nose irritation, a feeling of drunkenness, dyspnea, nausea, headache, ataxia, in the worst cases eventually leading to myoclonus, confusion, somnolence, coma and convulsions have been described (6-8). These symptoms have been reproduced in human and animal experiments which required very high exposure levels, especially if the exposure duration was limited in time (9-10). In the occupational setting high airborne solvent concentrations, which may increase the risk of acute intoxication, can be encountered when the working conditions are related to confined spaces (e.g. cleaning of tanks or reactors) without personal protection, when large quantities are to be applied on broad surfaces, when the ventilation flow is in the direction of the breathing zone, or when solvent containing products are sprayed or applied in warm environments or are heated. In the acute stage of intoxication no special clinical, neurophysiological (EEG, evoked potentials) or radiological signs (CT, MRI) were found except if concomitant hypoxia was present, resulting in cerebral edema or infarction. Afterwards a discrete cortical-subcortical atrophy on CT or MRI scanning was reported in some cases (11). Slowing of EEG activity was frequently seen in the acute stage. Only in such cases persistent cognitive deficit remained afterwards (12) and the presence of deficits in neuropsychological testing shortly after the intoxication seemed to predict a bad prognosis (6, 8). In conclusion, recovery after an acute intoxication with solvents can be uneventfully, but in several cases persisting mild to severe chronic encephalopathic syndromes were described (6-8). Therefore, timely testing of basic neuropsychological functions (e.g. concentration ability, memory, psychomotor accuracy and speed, and conceptual ability and speed) is necessary for an adequate evaluation of these patients. Acute solvent intoxication in which the solvent is metabolized to carbon monoxide (e.g. methylene chloride or methanol) produces the typical pattern of retinal degeneration and infarction in the basal ganglia in addition to the encephalopathy already described (13).

Chronic effects

In contrast to the acute intoxication situation, the debate about chronic neurotoxic effects of daily low to moderate solvent exposures is not yet settled. Gamberale and Hultengren (10) concluded that in occupational exposures not only the level of exposure, but also the duration of exposure must be crucial because in healthy volunteers a much higher concentration was needed in acute exposure conditions to induce the same symptoms. Organic psycho-syndromes with concentration and memory difficulties, diminished psychomotor speed, decreased mental flexibility,

mood changes, changes in personality, diffuse pain, and sleeping difficulties are usually described in workers who experienced working conditions which caused at least once symptoms of acute intoxication (14-16). Some of these cases had also signs of spasticity, ataxia, tremor or polyneuropathy (2, 7). But, numerous cross-sectional studies in healthy subjects exposed to solvents have shown dose-dependent subclinical effects on concentration, memory and psychomotor function (17-18), central and peripheral nerve conduction velocities (19), vestibular functioning (20), and slightly abnormal clinical neurological examinations (intentional and postural tremor, diminished distal peripheral reflexes, positive glabella reflex, increased body sway) (21-22). Even long-term exposure to low airborne exposure concentrations are likely to produce slight pre-narcotic or irritation symptoms like headache, nausea, inappropriate laughing or angeriness, dizziness, imbalance, and eye irritation (23). In addition, like for acute intoxications, chronic exposure conditions may lead to cortical and subcortical atrophy on CT-scan and diffuse diminished blood flow on Single Photon Emission Tomography (SPECT) examination (15). No difference was seen in the clinical picture regardless exposure had been to mixtures or to aromatic or aliphatic hydrocarbons (15-16, 24). The odds ratio that exposed workers develop a neuropsychiatric disease is estimated to be between 1.1 to 6.5 and increases with increasing duration and intensity of the exposure (25-29). Mikkelsen et al. (25) calculated that the risk starts to increase after 6 years of a time weighted average exposure (TWA) to 100 ppm white spirit. Viaene et al. (23) showed that pathological values on neurobehavioural tests were reached on average after 15 160 hours of exposure (equivalent to 8.6 years full time exposure) to a mean atmospheric styrene concentration of 155 mg/m³ during lamination tasks, corresponding to a 70 mg/m³ TWA concentration of styrene. Nine percent and 4% of the measurements were above the previous threshold limit value- short term exposure limit (TLV-STEL) value (426 mg/m³) and TLV-TWA value (213 mg/m³) (30) respectively. This would indicate that already the presence of only sporadic peak exposures may play a role in the development of chronic and/or persistent neurobehavioral effects. On average very low to low exposures without peak exposures have until now not proven to produce irreversible chronic neurotoxic effects (31).

Analysis of clinical cases indicated that psychomotor speed was the first neurobehavioral function to deteriorate after approximately ten years of exposure, followed by attention and memory (16). This has been corroborated in an epidemiological cross-sectional study in healthy workers exposed to styrene (23). If duration of exposure to moderate concentrations (approximating TLV-TWA-values or approximating 1 using the addition rule for mixtures according to the ACGIH) exceeds five years, subclinical

deficits of neurobehavioral functions could be detected in most studies (4), whereas overt clinical problems may not be expected before 10 years of full-time solvent exposure in these conditions. The determination of the duration of solvent exposure is seldom a problem, whereas the determination of the historical exposure concentration is often debatable.

Simultaneous alcohol consumption seems to have an additive neurotoxic effect (28) and workers with lower intelligence seem to be more susceptible (32) while other factors such as premorbid personality, legal claims, shift work, knowledge of the neurotoxic effects or union membership were not related to the development of organic psycho-syndrome (33).

To diagnose the presence of an organic psycho-syndrome (typical complaints and neurobehavioral deficits) it should have been developed during occupational solvent exposure and in the absence of any other etiological factor (34). No progression of the disease is seen after exposure is ceased, except if mood disorders secondary to chronic dysfunction become present. Most solvents may be detected in the air by human smell at concentrations much lower than those causing neurotoxic effects. The presence of a unpleasant smell is not always the clue to define high exposures. Therefore, a sound diagnosis will need a careful anamnesis into the occupational history and a comparison to known historical exposures in specific jobs. In addition, family and personal medical history, education, the course of development of complaints, clinical neurological examination, general examination and serum analysis, EEG, brain MRI, neuropsychological testing and polysomnography must complete the examination.

There is no effective therapy available. We have made some trials in subjects [with e.g. L-dopa and dopa-agonists, selective serotonin reuptake inhibitors (SSRIs), noradrenergic reuptake inhibitors, amfetamines, GABA-ergic medicines, case-reports not published] on the basis of animal studies showing neurotoxic actions of solvents on GABA-ergic, noradrenergic, dopaminergic and serotonergic neurotransmitter systems (35). These trials were not blinded and carried out in few patients for whom another rationale as to these therapies existed. None of these agents, except amfetamines, seemed to have any potential to increase the neurobehavioral performance, although secondary problems could be improved (e.g. depression with SSRIs; restless legs due to slight polyneuropathies with L-dopa and dopa-agonists; chronic diffuse muscle pain with amitriptiline or mirtazapine, baclofen, tetrazepam or newer anti-epileptic drugs; abnormal involuntary movements during sleep with clonazepam or L-dopa; sleeping problems with sedative antidepressants e.g. mirtazapine or trazodone). Amfetamines have to be prescribed with precaution

and in a strictly controlled therapeutical situations. We found cognitive behavioral therapy valid in learning OPS patient to adapt to their handicap, although mostly no effect on working ability could be obtained (not published). A neurotoxicological expertise center in Geel (Belgium) will start to study if the combination of cognitive behavioral therapy, medication, ergological revalidation and early personal counseling towards job ability may be more successful in regaining more socio-economic functions.

Prevention

A first step to prevent organic psycho-syndrome is regular monitoring of exposure by ambient air measurements and/or biomonitoring (at end of work shift). Most of the time this will give information about mean exposure concentrations, but it does not seem sufficient to prevent the development of chronic neurotoxicity in the individual worker. As has been pointed out before, sporadic peak exposures may be crucial events in the development of chronic toxic encephalopathy. In an occupational hygiene study in workers exposed to styrene in a polyester ship-building plant, it has been shown in 9 out of 12 unprotected and highly exposed workers (1 hour of styrene exposure above 426 mg/m³ during a normal 8-hour working day) that biomonitoring results were within normal limits, thus not reflecting the potential hazardous exposure (36-37). Environmental monitoring, especially short-term peak exposure measurements are needed. Moreover, the "addition rule" to calculate exposure levels for mixtures must be applied to the environmental monitoring data (30). Indeed, a small survey on historical exposure data of four printing plants showed that, regardless exposure levels to the initial (mostly aromatic) solvents components dropped, the exposure to the cumulative dose increased in two plants from below 1 (addition rule) to twice this level over the period 1980-1995, in contrast to what was general believed (38).

A second approach to prevention is bio-effect monitoring. Occupational exposure to solvents causes complaints. The number of complaints is as well related to the level of the daily exposure (the higher the exposure the more complaints) as to the cumulative exposure (23). Therefore, monitoring of complaints can be used as a first screening method to define highly exposed workers (primary prevention) as well as workers who already developed a chronic solvent encephalopathy (screening for disease). Complaints indicating acute pre-narcotic effects and mucosal irritation are mostly indicative of high exposure conditions (drunkenness, dizziness, dyspnea, eye and nose irritation, nausea, headache, feelings of suffocation or fainting). It is easy to look in workers for pre-narcotic sensations during their work. If answered positively, more attention to working con-

ditions must be given, followed by working place inspection and environmental monitoring using the worst case approach. It must be noted that some highly exposed persons do not experience the excess of complaints normally associated with acute exposure, although they are as prone as others to develop chronic neurotoxic effects due to high cumulative exposure (23). Complaints indicating a clinical organic psycho-syndrome due to high cumulative exposure are concentration and memory difficulties, diminished endurance, sweating, diffuse muscle pains, "pin and needle" sensations in hands and feet, gait instability, sleeping problems, Useful questionnaires which are screening for chronic neurotoxic effects are the Q16 questionnaire (Scandinavian countries) (39) and the Dutch NSC-60 questionnaire (40). If abnormal scores on these questionnaires are obtained, a clinical evaluation of underlying disease is necessary and if organic psycho-syndrome is confirmed, removal from solvent exposure is absolutely indicated.

A third approach of prevention is based on a combination of questionnaire data, clinical neurological signs and computerized neurobehavioral test results, all three integrated with the estimated cumulative dose (NEUROSCREEN) (41). Testing can be performed in the frame of the yearly routine occupational health examination. If pathological scores are reached, the probability of neurological or psychiatric disease (not only organic psycho-syndrome) was found to be very high (42), which makes this system very promising for secondary prevention.

Pitfalls

Only one in four to five of the patients referred to us as OPS are indeed organic psycho-syndrome patients (referred by the unions, neurologists, psychiatrists, occupational health specialists, as well as general practitioners). In most cases the erroneous diagnosis is anxiety disorders which began after exposure ceased or which are linked to very low exposure conditions. With increasing general awareness of environmental hazards and knowledge of the potential toxic effects of solvents and other chemical substances, patients and medical care givers increasingly attribute a variety of non-neurological diseases or complaints to past or still ongoing solvent exposure, which in their opinion also can be classified under the terminology of organic psycho-syndrome. General anxiety disorders, schizophrenia, schizoid and hysterionic personality disorders, chronic invalidating generalized inflammation of sinuses, chronic (hereditary) myopathies, anal eczema, seborrheic eczema, allergies, COPD, psoriasis, vitamin deficiencies, etc. have all passed our consultation rooms.

All these chronic disease entities will give secondary mood or concentration and memory complaints due to chronic pain, sleep disturbance or social or other handicaps. Careful history of disease development and its relation to cumulative exposure is therefore strictly necessary.

Other psychiatric diseases

Mood problems (depression) are an essential part of the clinical picture of the organic psycho-syndrome (43). The WHO described mood changes as one of the first clinical signs of organic psycho-syndrome (OPS type 2a). Mood changes in combination with neurobehavioral performance deficits were classified as OPS type 2b (44) (type 1 = only mucosal irritation and general health complaints, type 3 = dementia due to solvent intoxication). Campagna et al. (45) showed that mood changes were dose-dependent and developed independently from the other neurotoxic effects of solvent exposure. Depression in solvent-exposed workers must be followed carefully, especially if no apparent etiological factors are available or if therapy resistance is noticed. Extensive neuropsychological testing is indicated in these cases. Bipolar disease was always excluded in case-control or cross-sectional studies investigating the influence of solvent exposure on mood disorders. This is due to the high impact of genetic predisposition, although the influence of environmental factors is still estimated to be 35% (46). Whether solvent exposure can modify cyclic disease fluctuation in bipolar disorder is unknown, and therefore no recommendations can be made towards exposure or not in these patients.

An increased risk for psychosis at older age may exist in retired formerly exposed workers (47). Psychosis has been frequently described in glue sniffers and in workers exposed to CS₂ (> 100 ppm) (48).

Although anxiety is one of the symptoms occurring in OPS patients (49), the general awareness of the environmental pollution has induced a sub-type of anxiety disorder, the multiple chemical sensitivity syndrome (50). An acute intoxication (or just contact) with one sort of chemical (stimulus) causes physical illness (skin eruptions, headache, feelings of oppression, nausea, sweating, palpitations, tremor, hyperventilation, and/or dizziness,...) (response). Every new contact with the chemical induces growing distress and anticipation anxiety will develop between exposure episodes. Gradually exposures to other chemical substances and to lower and lower doses and in the end even imagination of exposure will induce the symptoms and signs. A sequential learning process between stimulus and response is most probably the etiological factor so that behavioral desensitization

techniques are the preferential therapy. In rare cases, the acute intoxication through solvents has induced at that moment extreme feelings of anxiety (certitude of dying), resulting in the development of a posttraumatic stress disorder (PTSD) (51).

Neurodegenerative diseases

Neurodegenerative disorders like motor neuron disease (MND, degeneration of the α -motor neurons with progressive paralysis, causing death by suffocation after an average of 2.5 years), Parkinson's disease (PD, degeneration of the dopaminergic neurons in the *substantia nigra*), and Alzheimer dementia (AD, degeneration of the central cholinergic neurons, next to wide-spread degeneration of other central neurons) are linked to exogenous neurotoxicants (52-53). Until now only exposure to CS₂ (54-55), acrylamide (56), ethylene oxide (57), and methanol (13) have been linked with parkinsonism (tremor, bradykinesia, cogwheel rigidity, ataxia). Although some case-control and cross-sectional studies in printers have suggested a link between PD and solvent exposure (odds ratio about 2) (54-55), no definitive conclusion can be drawn. The same is true for AD (58). Some of the earlier studies in solvent-exposed workers reporting an increased risk in dementia are in reality describing organic psychosyndromes if compared to the DSM-IV (59) criteria of dementia (60-61). Only for MND, there is growing evidence that exposure to different classes of chemical substances (pesticides, heavy metals, solvents) may increase the risk of developing this devastating disease with a factor 2 to 3 (10 case-control studies, 7/10 showing an increased risk associated with solvent-exposed work) (4).

Although the association between occupational solvent exposure and neurodegenerative disorders is not fully understood and the etiological link may not be made in the individual patient, it seems unwise to expose vulnerable patients occupationally to potential neurotoxic chemicals. Definitive removal especially from high and moderate solvent exposure is in my opinion necessary. To illustrate this, we refer to one patient with MND in whom progression of disease stopped immediately after exposure ceased (follow-up four years) (62).

Sleep apnoea

Exposure to solvents may play a role in the number of sleep apnoeas (63) and in the occurrence of a sleep apnoea syndrome (SAS) (64-65).

The clinical picture of a SAS resembles very well the clinical picture of OPS (increasing problems with concentration and memory, headache especially in the morning, unrefreshing sleep, sleepiness during day time, anxiety, depression, irritability,...). Therefore, a polysomnography is frequently needed to make the differential diagnosis.

Epilepsy

Knowledge about the impact of solvent exposure on the occurrence of epileptic insults or the recurrence rate is lacking. Convulsions due to severe acute intoxications have been reported (2, 33) and epileptic discharges have been described on EEG recordings of OPS type 2b/ OPS type 3 patients (66). Some anesthetics have known epileptogenic properties (e.g. propofol) (67). Some specialist in solvent neurotoxicology state that "solvents can worsen an existing epileptic disease" (3). Although evidence is not yet available, it might be possible that solvent exposure can worsen epilepsy especially in the beginning of exposure, during long holidays or with changing exposures, due to influence on anti-epileptic drug metabolizing systems (cytochrome P450 system).

Multiple Sclerosis

The occurrence and disease progression of multiple sclerosis (MS) is most probably mediated by different influences co-operating consecutively or simultaneously (68). Genetic influences (polygenes), racial influences, viral infections, nutrition and environmental toxins may all play a role in the etiopathogenesis of MS. Landtblom (68) concluded that exposure to solvents resulted in surprisingly high odds ratios for MS (1.6 to 4.9). The pathophysiological factor could be the impact of solvents on membrane solubility, e.g. on the blood-brain barrier, or an immuno-modelling mechanism of action. Although no definitive conclusions can be made about the possible promoting role of solvents, one has to be cautious to continue solvent exposure in MS patients.

Peripheral Nervous System Effects

Polyneuropathy

Distal axonal polyneuropathy (PNP) is typically seen in exposures to carbon disulfide (69), acrylamide (70), *n*-hexane (71), methyl *n*-butyl ketone

(72), ethylene oxide (73), and trichloroethylene (74). Except for trichloroethylene (Tri), clinical PNP develops at lower exposure levels to these solvents than the toxic central nervous system effects. Moderate to low Tri exposure (35 ppm) during 20 years causes subclinical changes in cranial en peripheral nerves (75-76), but also increases the risk to develop a toxic encephalopathy (OR = 5.6) (77). Diminished factory function has also been described in solvent-exposed workers (80).

In case-reports of OPS patients (exposures to styrene, toluene, tetrachloroethylene, solvent mixtures) the co-existence of a clinical distal axonal PNP was regularly reported (7, 15, 33, 66). In addition, subclinical effects on distal nerve conduction in cross-sectional studies were described (19, 22). Although no definitive conclusion can be made, toxic effects on the peripheral nervous system seem to co-exist with the toxic effects on the central nervous system. Complaints of paresthesia, anesthesia or diminished strength in hands and feet, muscle cramps, gait instability in the dark, orthostatic hypotension,... may be symptoms of a PNP. Easy to perform screening questionnaires are available (78).

Color vision loss

Color vision loss can be very important, especially in paint mixers and printers. Blue-yellow dyschromatopsia has been reported in exposures to solvent mixtures (38, 79), perchloroethylene (81), toluene (82), carbon disulfide (69, 83) and styrene (84). Exposures seem to be moderate to high as most studies with lower exposures do not report defects (85-86). Screening with Lanthony D-15 panel may be too insensitive, while other tests as the 100-Hue test or computerized test systems are too complex to be used as a screening tool in occupational settings, but can be done by specialists if necessary (38).

Hearing loss

Rybak (87) reviewed all the data available. He concluded that solvent-exposed workers should be followed by audiometry, as solvents (especially in combination with noise) can cause an (additional) symmetrical dip on the higher frequencies. The same conclusion was made for animal data (88).

Conclusion

Workers exposed to solvents are at risk to develop a chronic toxic encephalopathy, although effects (promoting or etiological) on other cen-

tral and peripheral nervous system diseases may be possible. Careful monitoring of exposure (environmental monitoring and bio-monitoring) but also bio-effect monitoring is strictly needed. Improved screening and improved diagnosis will increase the need for combined neuropsychiatric and socio-economic revalidation programs, especially since therapy is not yet available.

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