SOLVENT NEUROTOXICITY

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Organic solvents are widely employed in industry and are used in large quantities across the world. A solvent can be defined as "a liquid that has the ability to dissolve, suspend or extract other materials, without chemical change to the material or solvent".[1] Organic solvents are so widely used in the modern world as to be ubiquitous and are employed in paints, pharmaceuticals, degreasants, adhesives, printing inks, pesticides, cosmetics, and household cleaners. Commonly used solvents include, isopropanol, toluene, xylene, solvent mixtures such as white spirits and the chlorinated solvents, methylene chloride, trichloroethylene, and perchloroethylene. In Europe alone, approximately 300 000 metric tonnes of chlorinated solvents are sold each year. The United Kingdom's Health and Safety Executive estimate that 8% of the working population regularly use organic solvents.[1] The largest end user is the coatings industry where solvents play an important role in the quality and durability of paints and varnishes. The volumes of organic solvents used in some industries, for example dry cleaning, are declining, largely due to equipment and process improvements. Increasingly solvents are recovered and recycled, partly in response to environmental controls on volatile organic compound (VOC) discharges.[2] In addition, environmental legislation has led to a growth in the use of water based paints both in North America and in Europe at the expense of more traditional, solvent based coatings.[3] The Montreal Protocol of 1987 was a landmark in environmental regulation[4] and led to the production of a number of ozone depleting solvents being restricted or phased out. The protocol arose from concerns about the adverse impact of some solvents, including chlorofluorocarbons, on tropospheric ozone. Recently, 1-bromopropane, a solvent introduced to replace ozone depleting agents such as 1,1,1-trichloroethane (methylchloroform), has been shown to be neurotoxic in humans.[5 6]

Solvents are volatile agents and, in general, occupational exposures occur by inhalation of solvent vapour (table 1). However, as discussed in a previous article[7] in this series, dermal exposure is important in some industries such as painting (see fig 1) and industrial degreasing. Dermal uptake may contribute a significant fraction of the total body burden of solvents in workers employed in these sectors; Semple gives the example of a worker whose dermal exposure to the solvent xylene would contribute more than 50% of their total body burden.[7]

ACUTE HEALTH EFFECTS

The acute health effects of organic solvents reflect their central nervous system effects and include headache, dizziness, and light-headedness progressing to unconsciousness, seizures, and death.[8] Eye, nose, and throat irritation may also occur with exposure to solvent mixtures.[9] Abuse of organic solvents remains a problem, especially among deprived youngsters who use lighter fuel, glues, and household chemicals to obtain a "high". While the abuse of adhesives has declined over time, other agents of abuse, such as butane lighter fuel, have increased as a proportion of all volatile substance abuse deaths.[10] Every year in the United Kingdom around 65 children die following such abuse.[11] From an occupational perspective workplace solvent exposure may progress to abuse in some workers.[12]

The hazards of acute exposure are well recognised but fatalities still occur where poor working practices create the conditions for intense exposure in confined spaces. In the United Kingdom six people died between 1985 and 1996 in incidents involving solvent degreasing tanks (see fig 2). A failure to appreciate the volatile nature of solvents and to take appropriate precautions can lead to a risk of fire and explosion. A number of tragedies have occurred where an ignition source has been used in a confined space in close proximity to solvent vapour with predictable, and sometimes fatal, results.

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LONG TERM HEALTH EFFECTS

A number of long term adverse effects of solvents have been described including leukaemia in benzene exposed workers,[13] scleroderma[14] (mixed solvents), and renal cancer in those exposed to chlorinated hydrocarbons.[15] While the association between benzene and leukaemia is well

Table 1 Occupations with exposure to solvents

Occupation	Intensity of solvent exposure
Dry cleaning, screen printing, rotogravure printing, industrial painting, manufacture of glass reinforced plastic, tile fixing	High exposure
House painting, mechanic, assembly processes using solvents, paint making, industrial degreaser	Moderate exposure
Petrol pump attendant, joiner/carpenter, chemical process operator, laboratory technician, cleaner using polishes	Low exposure

This list is not exhaustive but rather gives an indication of the likely intensity of exposure in a range of occupations. The actual solvent exposure is determined by a number of factors including which solvent is used, in what concentration, the method of use, adequacy of ventilation, and the personal protective equipment employed. For example, a house painter applying water based paint by brush in a well ventilated room will have considerably lower exposure than one spray painting high solvent paint in a poorly ventilated cellar.

Figure 1 Industrial spray painters may have significant dermal exposure to solvents. This is due both to overspray and to the use of solvents such as white spirits as cleaning agents. Note the paint mist shown here during spray painting inside a ship's compartment. (Photo courtesy of Dr J W Cherrie, Institute of Occupational Medicine, Edinburgh).

Figure 2 An industrial degreasing tank containing methylene chloride. This tank is fitted with a roller cover to reduce solvent vapour release into the work environment during operation. A number of workers have died when safe systems of work have not been observed during cleaning of such industrial degreasing units.

established, other solvent effects, such as those on the nervous system, are more controversial.[16] Early studies in Scandinavia suggested that long term, high level, solvent exposure might be associated with a syndrome of personality change, memory impairment, and neurological deficits variously termed chronic toxic encephalopathy (CTE), the psycho-organic syndrome or solvent neurotoxicity. Some termed this "Danish painter's syndrome" although there was little evidence that the syndrome was so restricted, either by geography or occupation. Several early studies had methodological flaws and have since been heavily criticised.[17] Weaknesses of these studies included poor quality exposure surrogates such as *ever/never* exposed and a failure to adjust for confounders such as age or pre-morbid IQ. It seems likely that some studies had significant biases and early attempts to reproduce these findings out with Scandinavia were unsuccessful,[18 19] casting doubt on the existence of this syndrome.

One of the many difficulties with early research into solvent neurotoxicity was the lack of an agreed definition of the syndrome. The Nordic Council of Ministers and the World Health Organisation sponsored a conference in 1985 in Denmark that produced a definition of solvent neurotoxicity, which was subsequently revised at a meeting in North Carolina later that year[20] (see table 2). These criteria are important not only for researchers but also for clinicians for several reasons. If a diagnosis of solvent neurotoxicity is established then withdrawal from exposure can prevent further harm to the individual worker. Secondly, these criteria indicate likely prognosis and so are helpful in advising both the worker and their primary care physician. Thirdly, such a diagnosis can alert the employer to the need for improved workplace hygiene measures and so protect other workers.

Understandably there was considerable concern in the 1980s that solvents might affect workers' health. The Orebro Q16 questionnaire[21] was developed in response to the need for a tool to help occupational physicians identify those exposed workers requiring specialist assessment. Two validation studies carried out in the late 1990s found poor agreement between Q16 scores and psychometric test performance, so calling into question the Q16's use as a screening tool.[22 23]

More recent, well designed studies suggest that in heavily exposed workers, solvents may have subtle effects on cognitive function.[24] The cognitive domains affected by solvent exposures include attention, verbal memory, and visuospatial skills.[25 26] There is some evidence that solvent neurotoxicity is commoner among those with at least 10 years of occupational exposure to solvents. Whether the important determinant of adverse effects is the lifetime (cumulative) exposure, the intensity of exposure or peaks of exposure remains unclear. An area for further research is the development of better estimates of peak exposures to address this question.

The mechanism by which solvent mixtures exert their adverse effects on the nervous system is uncertain but it is suspected that the metabolism of solvents to toxic intermediates may be important. Attempts to identify the responsible agent are made more difficult as many workers

Table 2 Categorisation of solvent neurobehavioural effects[20]

Type		Symptoms
Type 1	Symptoms only	Symptoms include impaired memory, poor concentration, fatigue, and reduced motivation. Where exposure ceases these non-specific symptoms will resolve.
Type 2A	Sustained personality or mood change	Altered personality with lowered mood, reduced motivation, poor impulse control, anxiety, and irritability.
Type 2B	Impairment in intellectual function	Neuropsychological testing shows cognitive deficits affecting attention/concentration, visuospatial skills, and verbal memory. There may be minor neurological signs. If exposure ceases some recovery is likely but full recovery may not occur.
Type 3	Dementia	Cognitive impairment is often accompanied by neurological deficits. Nerve conduction studies, electromyography, or neuroradiology (CT or MRI scanning) may identify abnormalities. Deficits do not usually worsen if withdrawn from further exposure.

are exposed to industrial grade solvent mixtures of varying composition and purity. The heterogeneous nature of the chemicals classified as solvents[8] poses a problem when comparing the many studies of solvent health effects. There is some evidence that genetic polymorphisms affecting the activity of enzymes that metabolise foreign chemicals may influence the risk of solvent neurotoxicity.[27]

INVESTIGATION AND MANAGEMENT OF SUSPECTED SOLVENT NEUROTOXICITY

One challenge in assessing an individual who may have solvent neurotoxicity is to exclude other illnesses that can present with a similar clinical picture. For example, non-specific symptoms such as fatigue are very common and a number of conditions may be confused with type 1 solvent neurotoxicity (see table 2), such as depression or chronic fatigue syndrome. The diagnosis of solvent neurotoxicity is essentially one of exclusion. The occupational physician should suspect solvent neurotoxicity in a worker who reports such symptoms and has a history of heavy exposure to organic solvents through either their work or hobbies. A detailed occupational history focusing on exposure to solvents is required. History of acute solvent intoxication, for example one or more episodes of unconsciousness, indicates poor workplace controls and suggests heavy exposure. Compliance with occupational exposure limits for solvents may not be sufficient to protect all workers from long term adverse effects.[28]

Neuropsychological assessment is helpful in assessing reports of cognitive difficulties and can assist in identifying those with "pseudo dementia" due to depression. A neurological examination together with nerve conduction tests, where peripheral neuropathy is suspected, and magnetic resonance imaging (MRI) of the brain may be helpful in establishing the diagnosis. Brain imaging is useful, both in excluding other neurological conditions, and in identifying cerebral atrophy[29] or white matter lesions,[30] radiological changes that have been described in individuals with solvent neurotoxicity.

Management of an established case of solvent neurotoxicity is unsatisfactory as treatment is largely symptomatic. Withdrawal from further exposure is essential to prevent disease progression. The use of anxiolytics can be helpful in alleviating psychological distress, and antidepressants and psychological support can be beneficial if the worker is depressed.

The prognosis for solvent neurotoxicity is dependent on its severity. Mild cases (type 1) will usually resolve with removal from exposure, but in more severe cases (for example, type 2B), if exposure ceases the condition does not progress but equally may not improve.[31 32] There is some evidence that the number of workers newly diagnosed as suffering from solvent neurotoxicity has declined over the last two decades.[8 33] Improved workplace controls mean fewer workers are heavily exposed to solvents than in the past, and the declining incidence of solvent neurotoxicity in Europe and North America is encouraging. However, workers in organisations that lack an effective health and safety culture remain at risk.

NEURODEGENERATIVE DISEASES AND SOLVENTS

There has been concern that a number of neurodegenerative diseases might be associated with heavy workplace exposure to organic solvents. However, given the widespread use of solvents, such associations may simply be chance occurrences. Nonetheless the public health implications of such effects, if proven, would be considerable.

Parkinson's disease (PD) is a movement disorder that has been associated with solvent exposure in a number of studies,[34 36] although the evidence is not compelling. Perhaps the most persuasive study to date was a study of unusual design[37] which found that solvent exposed PD patients were on average three years younger and were less responsive to L-dopa than unexposed patients with PD.

Essential tremor (ET) is the commonest movement disorder, is of unknown aetiology, and affects between 1% and 2.2% of the population over the age of 60 although it may be over-diagnosed.[38] In severe cases the disease can lead to job change or early retirement.[39] Solvent exposures have been suggested as a possible risk factor for ET, although a large American study failed to show any association.[40]

The commonest neurodegenerative disease is Alzheimer's disease. Job title (which can be viewed as a crude marker for exposure) and solvent exposure have been studied as risk factors for Alzheimer's disease but with conflicting results. While some studies suggest that blue-collar work[41 42] or solvent exposures[43] are risk factors, others do not.[44 45] It may be that solvent exposure is a marker for low pre-morbid intelligence that is, itself, a risk factor for dementia.[46]

Motor neurone disease (MND) or amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with an incidence of 1–2 cases per 100 000 people per year and a lifetime prevalence of 0.1 per 1000 of the UK population.[47] Many of the criticisms of studies of solvents as risk factors for Alzheimer's disease can be levelled at the small number of studies of solvent exposures as risk factors for MND. These include low quality exposure estimation,[48 49] imprecise diagnostic criteria,[49] and study of prevalent[48] rather than incident cases. A recent UK case-control study that employed death certificate data from an occupational pension scheme

together with occupational histories failed to show an association between solvent exposed employment and MND.[50] Even the best designed incident studies[51 52] have given conflicting results.

Multiple sclerosis (MS) has been linked to solvent exposure in a number of case reports[53] and case-control studies.[54–56] A Swedish meta-analysis[57] generated a pooled relative risk (RR) of 1.7–2.6 for solvent exposures and MS. However, a subsequent cohort study in Denmark[58] failed to find any evidence of an association, although that study employed occupation at cohort inception as a surrogate for solvent exposure. This imprecise marker of occupational solvent exposure may have obscured any association. On the other hand, some positive studies may have been confounded by other factors that have, themselves, been linked to MS (for example, sunlight exposure).[59] A large prospective study might clarify whether solvents are, indeed, risk factors for MS.

One difficulty is that several of these neurodegenerative conditions (for example, Parkinson's disease) are not single disease entities but a heterogeneous group of clinically similar conditions. It may be that some individuals have solvent induced neurodegeneration but these are lost among the majority of sufferers whose condition is not due to solvents.

PERIPHERAL NEUROPATHY AND SOLVENTS

There is strong evidence that some solvents may cause peripheral neuropathy. Clinically this presents with symptoms in the feet and lower legs before progressing to involve the hands. Symptoms are those of a sensorimotor neuropathy with altered sensation, loss of vibration perception, impaired proprioception leading to impaired balance, and distal muscle wasting. The most researched agent is *n*-hexane (the *n* stands for "normal" hexane to distinguish it from the isoforms of hexane, 3-methyl pentane, 2-methyl pentane, and 2,3-methyl butane) which has been associated with outbreaks of peripheral neuropathy in furniture manufacture,[60] printers,[61] and shoe makers.[62] Methyl *n*-butyl ketone was shown to be neurotoxic following an outbreak of peripheral neuropathy in an Ohio textile printing plant.[63] Subsequent animal studies showed that *n*-hexane and methyl *n*-butyl ketone share a common neurotoxic metabolite, 2,5-hexanedione.[64] There is some evidence that commonly used ketones (acetone, methyl ethyl ketone, and methyl isobutyl ketone) may potentiate the toxicity of *n*-hexane and other solvents, a finding that raises doubts about the widely used method of calculating mixed solvent exposures based on the additivity of exposures.[65] Other solvents have been implicated as peripheral neurotoxins including carbon disulphide,[66] styrene,[67] and 1,1,1-trichloroethane.[68] The evidence for these latter associations is relatively weak; given the wide usage of some of these substances many more cases of peripheral neuropathy might be anticipated.

SPECIAL SENSES AND SOLVENTS

The special senses, taste, sight, and smell may be affected by exposure to solvents. Many, but by no means all, studies have found mild acquired colour vision losses in solvent exposed workers.[69] The impairment is generally subtle, and affected workers are typically unaware of altered colour perception. Unlike congenital colour "blindness", which is commoner in men and is usually a protan or deutan defect (red–green colour blindness), acquired colour vision losses are frequently tritan, sometimes termed "blue–yellow" loss. These tritan losses may progress to affect red–green colour vision. The practical relevance of such sub-clinical effects is questionable and at present these findings remain in the realm of research.

Altered sense of smell has been described in solvent exposed groups.[70] Anosmia may have an impact on safety where workers lose the ability to detect chemical releases.

Animal studies using rats have found that some solvents are ototoxic,[71] and co-exposures to noise and solvents lead to greater hearing loss than would be expected due to noise exposure alone.[72] The difficulties of replicating these studies in humans are considerable, not least owing to problems in the retrospective estimation of noise exposure. Nonetheless epidemiological studies have shown that some aromatic solvents may act synergistically with noise to impair hearing in exposed workers.[73–75]

Key points

- Inhalation is the main exposure route for organic solvents
- Dermal exposure to certain solvents may be an important exposure route in some work settings
- Heavy, long term, exposure to solvents is associated with subtle neuropsychological effects
- Solvents, such as styrene, may cause sub-clinical colour vision losses
- Solvents affect hearing and may act synergistically with noise exposures

PREVENTION OF SOLVENT NEUROTOXICITY

Good occupational hygiene practice is the mainstay of managing solvent exposures: substitution with water based agents, engineering controls such as adequate local exhaust ventilation, administrative controls (for example, supervisors ensuring the storage of solvents in sealed containers when not in use), worker education, and finally the use of appropriate personal protective equipment that is fit for purpose. Monitoring of workers' solvent exposure by personal sampling and biological surveillance may be indicated.

CONCLUSION

Heavy solvent exposure is associated with a number of adverse effects including mild cognitive impairment, hearing loss, and sub-clinical colour vision deficits. Whether these agents are risk factors for neurodegenerative diseases is less clear. Solvents are, and will remain, important agents in the workplace. Occupational physicians should continue to urge employers and the self-employed to adopt appropriate control measures to minimise solvent exposures and so protect health and safety.

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QUESTIONS (SEE ANSWERS ON P 179)

Please indicate if the following statements are true or false.

(1) Acute effects of solvents include:
  (a) Photophobia
  (b) Urticaria
  (c) Nausea
  (d) Dizziness
  (e) Headache

(2) Long term exposure to solvents may cause:
  (a) Mild cognitive impairment
  (b) Impaired balance
  (c) Altered sense of smell
  (d) Hearing loss
  (e) "Pseudo dementia"

(3) Long term solvent exposure is associated with:
  (a) Acquired deutan colour vision loss
  (b) Macular degeneration
  (c) Congenital colour vision loss
  (d) Achromatopsia
  (e) Acquired tritan colour vision loss

(4) Exposure to *n*-hexane may cause:
  (a) Impaired vibration perception
  (b) Hyperaesthesia
  (c) Tingling in the feet
  (d) Proximal muscle wasting
  (e) Impaired proprioception

(5) Control measures to reduce solvent exposures include:
  (a) Improved general ventilation
  (b) Substitution of solvent based paints with water based paints
  (c) Use of nuisance dust masks
  (d) Provision of suitable gloves
  (e) Use of non-solvent hand cleansers