

Organic solvent neurotoxicity

Facts and research needs

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SPENCER PS, SCHAUMBURG HH. Organic solvent neurotoxicity: Facts and research needs. *Scand J Work Environ Health* 11 (1985): suppl 1, 53–60. While many organic solvents are, in large doses, capable of inducing an acute, reversible narcotic state, few unequivocally induce chronic, long-lasting, or irreversible changes in nervous system structure and/or function. For organic solvents with proved neurotoxic properties, the type of neurological damage is closely related to the structure of the chemical agent, while the degree of impairment and the extent of reversibility are related to the potency, dose, and duration of exposure. Examples include solvents containing *n*-hexane or methyl *n*-butyl ketone, which have caused many cases of occupational neuropathy. Chronic inhalation abuse of pure toluene produces irreversible cerebellar, brainstem, and pyramidal-tract dysfunction, but comparable changes have not been found in solvent workers occupationally exposed to toluene. Ototoxicity is found in experimental animals exposed to toluene, xylene, or styrene. Impure trichloroethylene has a predilection for damaging the trigeminal nerve; dichloroacetylene, a breakdown product of trichloroethylene, is probably responsible for this neurotoxic property. Prolonged occupational exposure to mixed solvents, notably white spirit, has been reported to induce a mild, nonprogressive dementing illness with or without peripheral nerve dysfunction, but supporting data from neuropathological and experimental animal studies are lacking. Many other solvents have been reported to induce adverse effects in workers. The pivotal biological role of the nervous system and its vulnerability to selected organic solvents widely used in industry underline the urgent need for further clinical and experimental research on this problem.

Key terms: animal studies, clinical studies, drug abuse, encephalopathy, human neurotoxicity, neuropathy, occupational exposure, organic solvents, ototoxicity.

There is growing concern that repeated human exposure to organic solvents may result in irreversible structural damage to the nervous system, manifest as changes in behavior and neurological function. Much of the impetus for the present concern comes from Denmark, Sweden, and Finland, where it seems widely accepted that prolonged occupational exposure to solvent mixtures of various types precipitates an irreversible organic mental syndrome characterized by personality change, impairment of memory, and intellectual decline, with attendant mild dysfunction of the autonomic and somatic divisions of the peripheral nervous system. This paper examines the evidence for the assertion that organic solvents are neurotoxic and identifies critical areas for further investigation.

Criteria for neurotoxicity

Three questions must be answered affirmatively before a solvent can be accepted as a human neurotoxicant. Does the substance or mixture produce a consis-

tent pattern of neurological dysfunction in humans? Can this entity be induced in animals under comparable exposure conditions? Are there reproducible lesions in the nervous system or special sense organs of exposed humans and/or animals, and do these abnormalities satisfactorily account for the neurobehavioral dysfunction? Failure to satisfy any of these criteria leaves room for doubt that the suspect agent is capable of impairing the structure or function of the nervous system.

Proved human neurotoxic solvents

Five solvents that meet the criteria for acceptance as proved human neurotoxicants are listed in table 1. Omitted from this list are methanol and ethanol because their respective adverse visual and neurological effects are well known. Several other solvents are included that are claimed to be neurotoxic, as well as others which merit testing because of structure-activity relationships to neurotoxic substances or for other reasons.

Carbon disulfide

Used as a solvent for oils, waxes and resins, as a fumigant, and as a component in the manufacture of viscose rayon, carbon disulfide is an irritant and a

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Table 1. Single and mixed organic solvents implicated as human neurotoxicants. (A = animal, H = human)

Substance	Effect
<i>Proved human neurotoxicants</i>	
Carbon disulfide	Psychosis (H), neuropathy (H, A), tardive parkinsonism (H)
<i>n</i> -Hexane $\pm$ methyl ethyl ketone (MEK)	Peripheral neuropathy (H, A)
Methyl <i>n</i> -butyl ketone $\pm$ MEK	Peripheral neuropathy (H, A)
Toluene (substance abuse only)	Auditory (A), brainstem, cerebellar, pyramidal and other types of irreversible brain dysfunction (H)
Impure trichloroethylene (TCE) (from dichloroacetylene)	Trigeminal neuralgia (H), transverse myelopathy (H?), brainstem degeneration (A)
<i>Proposed human neurotoxicants</i>	
Diethyl ether	Anorexia? (H)
Ethylene chloride	Encephalopathy, tremor? (H)
Nitrobenzene	Limb numbness? (H)
Pyridine	Facial paralysis? (H)
Styrene	Ototoxicity (A), neuropathy (H?)
Tetrachloroethane	Neuropathy? (H)
TCE $\pm$ perchloroethylene	Organic mental syndrome? (H)
Xylene	Ototoxicity (A), organic mental syndrome (H?)
White spirit	Organic mental syndrome (H)
Various mixed solvents	Organic mental syndrome? (H)
<i>Agents meriting investigation</i>	
Chromogenic aromatic hydrocarbons	See table 2
Methylene chloride	Carbon monoxide metabolite

metabolic poison. Systemic effects include gastrointestinal, cardiovascular, renal, endocrine, and nervous-system disorders, including psychosis and peripheral neuropathy (48). Susceptibility to parkinsonism has also been reported (58). The recognition of these neurological disorders early in this century led to improved industrial hygiene and reduced concentrations of carbon disulfide in the workplace. While high airborne levels still may be found in viscose rayon plants located in certain developing countries, concentrations of 10–30 ppm (with brief excursions up to 100 ppm) are usually encountered in the West. These levels meet the legal limits for human occupational exposure set in the United States (3), but it is unclear whether they are low enough to prevent chronic human neurological dysfunction. In recent years, several groups of investigators have collected evidence of psychomotor deficits and impaired intellectual function in workers exposed to low airborne levels of carbon disulfide (10, 18, 22). Other studies cite evidence of subclinical peripheral neuropathy (29, 49, 57). Taken together these studies clearly question the safety of the present limits of workplace exposure to carbon disulfide.

Experimental animal studies confirm that carbon disulfide is a neurotoxicant. Dogs exposed subchronically to high airborne levels exhibit behavioral disturbances (apprehension, excitation, aggression), ataxia, choreiform movements, loss of limb position

sense, and paralysis (10). Electrophysiological studies demonstrate nerve conduction abnormalities in chronically intoxicated rats and rabbits, as in humans with carbon disulfide neuropathy (48). Morphological studies reveal axonal swellings filled with neurofilaments and a distal degeneration of peripheral nerves and long spinal-cord tracts (central-peripheral distal axonopathy) (56). Degenerative changes have also been reported in cerebral and cerebellar cortex and in basal ganglia (48).

These data provide a solid basis to indict carbon disulfide as a chronic human neurotoxicant. There is a long history of a uniform pattern of neurological dysfunction (psychosis and neuropathy). These disorders can be reproduced in experimental species, and pathophysiological studies of humans and animals provide a rational explanation for the functional abnormalities. Further clinical and experimental animal studies are required to establish an acceptable limit for human exposure to carbon disulfide.

Normal hexane and other alkanes

n-Hexane is also an established chronic human neurotoxicant. Outbreaks of neurological disease — always associated with solvent mixtures containing *n*-hexane — have occurred both in the workplace and in individuals abusively inhaling the compound (1, 25). Changes in higher mental function are usually absent, and neurological dysfunction is confined to a sensorimotor or motor peripheral neuropathy. The more severely affected solvent sniffers occasionally also display cranial-nerve and autonomic dysfunction (1). Although neuropathy may progress for a short time after exposure has ceased, the disorder slowly regresses thereafter, and partial or complete recovery is the rule.

Pathophysiological changes in humans with neuropathy are also reproducible in animals exposed to pure *n*-hexane (46). The degree of neurological impairment in rats increases as a function of dose and may be substantially potentiated by concurrent exposure to methyl ethyl ketone. (See the next section.) Neuropathological studies reveal a pattern of abnormality in the spinal cord and peripheral nerves similar to that found in animals with carbon disulfide neuropathy (53).

n-Hexane is metabolized in animals and humans to a gamma diketone, 2,5-hexanedione, a compound with substantially greater neurotoxic potency than the parent alkane (11). Potency tends to decrease in gamma-diketones with longer carbon backbones, but the morphological pattern of experimental neuropathy is identical (39). Since alkanes normally undergo subterminal carbon oxidation, the likelihood of producing neurotoxic levels of gammadiketone metabolites from alkanes higher in the series than *n*-hexane is unlikely. Shorter chain alkanes (pentane) and hexane isomers free of *n*-hexane also fail

to produce the appropriate metabolite and do not induce neuropathy in experimental animals (54). For this reason, therefore, *n*-hexane is unique among the alkanes in producing peripheral neuropathy in humans.

Ketones

An identical pattern of neurological damage occurs in humans and experimental animals chronically exposed to methyl *n*-butyl ketone (35, 54). An oxidative metabolite of *n*-hexane, and itself metabolized to 2,5-hexanedione, methyl *n*-butyl ketone displays an experimental neurotoxic potency between that of its two metabolic relatives (39). Workers exposed to mixtures containing the compound develop a neuropathy essentially indistinguishable from that seen in occupational *n*-hexane intoxication (54). Experimental animal studies demonstrate that the two disorders produce indistinguishable patterns of long-tract damage in peripheral nerves and the spinal cord (53).

Ketonic solvents that do not form gamma-diketone metabolites, such as acetone, methyl isobutyl ketone, methyl *n*-amyl ketone, and methyl ethyl ketone, fail to induce neuropathy in chronically exposed animals (54). However, methyl ethyl ketone is able to potentiate the neurotoxic potency of both *n*-hexane and methyl *n*-butyl ketone in rats and probably in humans (1). Occupational exposure to the mixed solvents should therefore be avoided.

Trichloroethylene (and perchloroethylene)

Trichloroethylene was recognized as an industrial hazard over 50 years ago (14). The slowly reversible trigeminal neuropathy associated with trichloroethylene intoxication became so well accepted that, for a

time, intentional exposure to the compound was considered a useful treatment for tic douloureux. Cranial neuropathies also occurred when trichloroethylene was employed as an inhalant analgesic-anesthetic for brief dental and obstetrical procedures (15). Unlike the peripheral neuropathies associated with carbon disulfide, *n*-hexane and methyl *n*-butyl ketone, trichloroethylene neuropathy is associated with sensory loss (facial dysesthesia and numbness) and motor weakness (muscles of mastication) in the distribution of the trigeminal nerve. Lower cranial and optic nerves may also be involved (14). These types of cranial neuropathies are now attributed to a spontaneous decomposition product of trichloroethylene, ie, dichloroacetylene. This agent disrupts the appropriate region of the brainstem of experimentally treated animals and is therefore possibly responsible for the neurotoxic properties of trichloroethylene (47).

Short-term exposure to narcotizing levels of trichloroethylene in the industrial setting has also been reported to induce transverse myelopathy (42). While this report is unconfirmed, it is interesting to note the experimental production of transverse myelopathy in the rat with dichloroacetate, a possible metabolite of trichloroethylene/dichloroacetylene. This phenomenon was characterized by a focus of demyelination in the upper thoracic region which disrupted all the white matter, save the dorsal columns (figure 1). Remyelination of denuded axons took place during the period of intoxication and was accomplished by both oligodendrocytes and peripheral myelinating (Schwann) cells that had invaded the lesion (figure 2) (51).

Long-term, low-level exposure to trichloroethylene has also been reported to produce adverse neurological and neuropsychiatric effects, including tremor, giddiness, increased lacrimation, reddening of the skin, decreased sensitivity of the hands, alcohol intolerance, neurasthenia and anxiety, bradycardia,

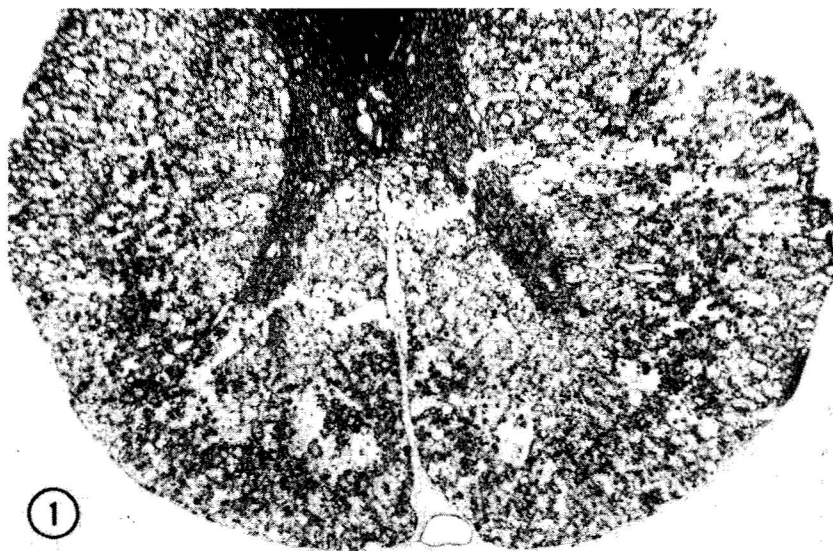


Figure 1. Cross-section of the upper thoracic region of the spinal cord of a rat after 13 weeks of oral treatment with $2 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ sodium dichloroacetate. Only the dorsal columns have been spared extensive demyelination. Dorsal and ventral roots are unaffected (magnification 10X).

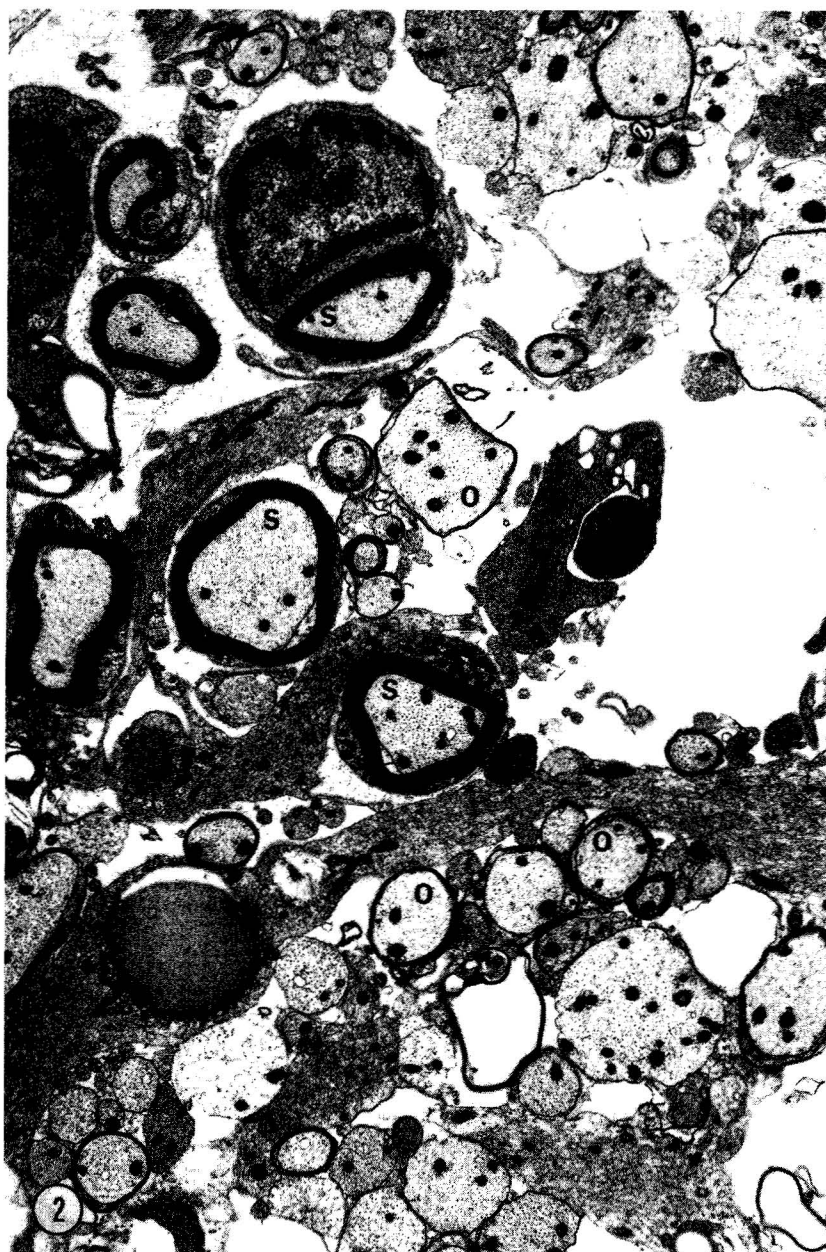


Figure 2. Remyelination by oligodendrocytes (o) and Schwann cells (s) deep in the spinal cord of a rat treated for 25 weeks with oral sodium dichloroacetate (magnification 5 230X).

and insomnia (2, 6, 21, 33, 43). These disorders reportedly tend to become more severe with length of employment and degree of exposure. However, there are no adequate epidemiologic studies of worker populations and no experimental animal models of this condition. Anger & Johnson (3) concluded that there was no compelling evidence that exposure to trichloroethylene at or below 300 ppm has an adverse neurobehavioral effect.

Perchloroethylene, now widely used as a substitute for trichloroethylene in the dry cleaning of fabrics

and degreasing of fabricated metal parts, reportedly produces similar neurasthenic effects, including long-lasting changes in personality and recent memory (19). Comparable changes, as well as trigeminal sensory defects, have been reported in individuals exposed to mixtures of trichloroethylene and perchloroethylene (4, 27). Additional studies of human populations and experimental animals are required to evaluate the suggestion that chronic occupational exposure to trichloroethylene and/or perchloroethylene precipitates irreversible changes in brain function.

Toluene

A consistent pattern of neurological damage has been reported in individuals repeatedly inhaling pure toluene for its euphoric properties (7, 20, 28, 31, 59). Progressive and irreversible changes in brain structure and function also have been found in others deliberately inhaling toluene-based paints (30, 36, 44, 45). Comparable deficits have not been reported in workers occupationally exposed to toluene for 3–32 years at levels close to the hygienic standard of 100 ppm.

Brain damage induced by toluene abuse seems to appear insidiously after 1–20 years of repeated exposure to estimated concentrations of several thousand parts per million. Early neurobehavioral changes consist of anxiety, irritability, mood swings, and forgetfulness. A coarse tremor appears in the hands and subsequently may spread to involve the arms, lower limbs, trunk, and neck. With further exposure, the victim develops nystagmus, slurring of speech, bilateral hearing impairment, titubation, and a wide-based ataxic gait. Psychological testing reveals impairment of cognitive function, emotional instability, and short-term memory loss, and neurological examination shows frontal release signs and pyramidal dysfunction. Ventricular dilatation and widening of the cortical sulci, especially in the frontal or temporal cortex, together with brainstem and/or cerebellar atrophy, are evident when studied by pneumoencephalography or computed tomography. Peripheral neuropathy is not a feature of toluene abuse.

Few animal studies have examined the neurotoxic properties of toluene. Cortical and cerebellar degeneration was found in dogs receiving repeated intravenous injections of the compound, where blood levels approximated the highest quantities reported in solvent addicts (30). High-frequency hearing loss and appropriate cochlear changes were found in weanling rats exposed for 14 h/d, 7 d/week for 5 weeks to 1 200–1 400 ppm of toluene (40, 41), but no solvent-induced alterations in the structure of brain or peripheral nerves were seen in young adult animals treated with 1 500 ppm 6 h/d, 5 d/week for 6 months (50).

Chronic neurobehavioral disorders have not been demonstrated in workers exposed to toluene; however, there have been no attempts to monitor auditory function. Recent Swedish studies of rotogravure printers exposed almost exclusively to toluene (50–150 ppm) for 3–32 years only revealed evidence of acute, reversible changes in brain function (12, 26, 55). Another study reported cerebellar deficits that increased in severity with time of occupational exposure to solvents containing up to 20 % aromatic hydrocarbons (mostly xylene and toluene) (27), but this is insufficient evidence to indict toluene.

Further research on toluene is required to determine exposure levels that lead to irreversible neurobehavioral changes. Two lines may prove fruitful, ie,

epidemiologic surveys focused on the early signs of chronic neurological dysfunction (ie, high-frequency hearing loss, abnormal mentation, hand tremor, ataxia, and slurred speech) and animal studies to determine the threshold for nervous system alterations and the interrelationship between these changes and circulating levels of toluene and its metabolites.

Possible human neurotoxic solvents and suspect agents

The remaining portion of this presentation deals with single or mixed solvents which require further investigation as possible human neurotoxins. Concern over these agents has arisen from the results of epidemiologic study, from structure-activity considerations, or, in one case (methylene chloride), the presence of an indirect neurotoxic metabolite. Included in this section is a large number of Scandinavian papers indicating various solvent mixtures as chronic human neurotoxicants. None of the agents presently fulfill the criteria for a human neurotoxicant as defined in the section Criteria for Neurotoxicity.

Monocyclic and dicyclic aromatic hydrocarbons

Over 25 years ago, Gerarde (17) reported that the parenteral administration of several monocyclic and dicyclic aromatic hydrocarbons resulted in a blue discoloration of tissues and/or urine (table 2). Excretion of green-colored urine has also been noted for humans occupationally exposed to tetralin (8). These observations were of only academic interest until the discovery that a chromogenic derivative of one of these compounds, 8-acetyl-1,1,4,4-tetramethyl-7-ethyl-1,2,3,4-tetralin, produced severe damage to the brain, spinal cord, and peripheral nerves of experimental animals (52). Affected rats became excitable and irritable, then ataxic and weak in the hind limbs. The further experimental finding that methyl substitution of the 7-ethyl group blocked both the chromogenic and neurotoxic properties of this molecule led to concern that these two properties may be interlinked (50). This notion, plus the observation that certain compounds listed in table 2 have been reported to produce chronic neurological changes in the occupational setting, indicate that these sub-

Table 2. List of chromogenic aromatic hydrocarbons.*

Monocyclic	Dicyclic
Benzene	Indane
o-Xylene	Indene
o-Ethyltoluene	Tetralin
o-Diethylbenzene	Diphenyl
m-Diethylbenzene	Diphenylmethane
o-Diisopropylbenzene	1-Methylnaphthalene
Triethylbenzene	1-Ethyl-naphthalene
Diethyldiisopropylbenzene	2-Ethyl-naphthalene

* Rats receiving a single subcutaneous dose of 5 ml/kg reportedly develop blue discoloration of tissues and/or urine [reproduced from Gerarde (17)].

stances merit further study for possible neurotoxic properties.

Xylene(s)

Commercial xylene is predominantly composed of meta-xylene, but also contains para-xylene, ortho-xylene, and ethyl benzene (table 2). Acute effects of occupational exposure to xylene are well described, and several papers have reported an organic brain syndrome in workers exposed to solvent mixtures containing xylene (23, 24, 34). There are no reports of these chronic changes occurring in individuals exposed to the pure compound and no experimental animal studies to support this notion. Xylenes have been found to exhibit greater ototoxic potency than toluene in weanling rats (40). Further studies are clearly merited.

Solvent mixtures

Several recent papers, predominantly from Denmark, Finland, and Sweden, have claimed that prolonged occupational exposure to various solvent mixtures induces irreversible changes in neurological function characterized by personality alteration, memory loss, intellectual decline, autonomic dysfunction, and low-grade peripheral neuropathy. This type of mild dementing illness (psychoorganic syndrome, mental organic syndrome, chronic toxic encephalopathy) is considered to develop after ten or more years of occupational exposure, although one recent report suggested that the period may be as short as three years (16). The condition is stated to be progressive during exposure and to plateau once exposure has terminated. Most studies on this subject have used epidemiologic techniques to compare and contrast findings in solvent-exposed and reference groups. Few provide an analysis of the solvent mixture to which the workers were exposed, and some studies were conducted on subjects experiencing the acute effects of the solvent mixture under study. A number of investigations lacked an adequate reference group. Many have relied on self-administered questionnaires, and others on psychometric tests, neurological examination, and various clinical tests to assess neural function. Disparate findings are often grouped together, and reliance is placed on statistical techniques to yield small differences between those exposed and the referents. There are no neuropathological studies of this entity and no animal models. In short, while there is cause for concern and a clear need for further research, compelling data are unavailable.

The most disturbing reports of organic mental syndrome have come from uncontrolled studies of Danish house painters occupationally exposed to white spirit (5, 9). Many of the subjects found to have intellectual impairment also displayed significantly widened cortical sulci or ventricular enlargement both at the time of examination and after two

years of follow-up. These observations are strengthened by retrospective findings of a two to three times greater incidence of dementing illness (as a cause for disability pension) among male painters than among bricklayers (37). The exact composition of white spirit is unknown, although mineral spirit (thought to be homologous) is said to consist of 80–86 % saturated hydrocarbons (predominantly C9–C12), 13–19 % aromatics, and 1 % olefins (38). The composition of the aromatic component is of special interest because repeated exposure to some of these compounds appears to precipitate changes in brain structure and/or function. (See the section Monocyclic and Dicyclic Aromatic Hydrocarbons.) Although product reformulation has now reduced occupational exposure to white spirit, it would be a missed opportunity not to conduct experimental animal studies to determine if this solvent mixture has chronic neurotoxic properties and, if so, what they are.

Other compounds

There are many other solvents and mixtures alleged to have chronic neurotoxic effects in humans, but compelling evidence again is lacking. Tetrachloroethane and styrene have been reported to cause occupational neuropathy, and experimental studies have demonstrated styrene to be ototoxic to weanling rats (41). Contact with nitrobenzene allegedly produces headache, giddiness, tinnitus, and limb numbness. Chronic exposure to ethylene chloride reportedly induces encephalopathic symptoms and hand tremor. Occupational exposure to diethyl ether has been associated with anorexia, increased thirst, and excessive fatigue. Facial paralysis, abnormal eye movements, and unsteadiness of gait apparently occurred rarely in individuals exposed to pyridine (8). These reports illustrate the range of neurological effects that have been associated with solvent exposure and underline the need for further study of these and many other solvent agents. Attention also should be given to methylene chloride, a very widely used solvent which forms carbon monoxide (a potent indirect neurotoxicant) on metabolic breakdown. Significant concentrations of carboxyhemoglobin have been recorded in workers using methylene chloride, and such concentrations are likely to complement the effects of other sources of carbon monoxide, notably tobacco smoking (13). The effects of chronic low-level exposure to carbon monoxide are not understood and require extensive experimental investigation (3).

Principles for future research

This brief survey demonstrates that certain aliphatic and aromatic solvents are proved neurotoxicants in humans and animals. Some of these agents have caused outbreaks of neurological disease in the occupational setting; others have been tragically discovered by drug abusers. Many other solvents and solvent mixtures are suspect human neurotoxicants

and, remarkably, the majority of solvents in daily use has yet to be tested for chronic neurological effects in experimental animals.

Several principles can be deduced from our limited knowledge of solvent neurotoxicity. First, it is apparent that many solvents induce short-term changes in brain function which, if hypoxia is avoided, will generally result in rapid and total recovery. The acute neuroactive properties of solvents provide no indication of likely chronic neurotoxicity, and there is often no relationship between the nature or mechanism of these effects. Acute effects on brain function are often related to the parent compound (eg, *n*-hexane narcosis), while a chronic effect may be associated with a metabolite (eg, 2,5-hexanedione neuropathy). Chronic neurological dysfunction is usually associated with structural changes in nervous tissue, and the type of damage is often specific for individual compounds. (A general type of chronic effect — such as organic mental syndrome — from a number of organic solvents has yet to be demonstrated.) The degree of neurobehavioral change produced by neurotoxic solvents is the most closely related to dose and duration of exposure, and most individuals subjected to a neurotoxic dose will develop a similar degree and type of neurological deficit. However, individuals with renal or hepatic dysfunction, metabolic conditions associated with neural dysfunction (eg, diabetes), or exposure to substances (including ethanol) with neurotoxic properties or with effects on solvent metabolism *a priori* may display special vulnerability to organic solvents. In two cases, one solvent (methyl ethyl ketone) is known to alter the neurotoxic potency of others (*n*-hexane, methyl *n*-butyl ketone). Cessation of exposure to a neurotoxic substance paradoxically may be associated with a period of intensified abnormality (“coasting”) prior to the onset of recovery. The degree of reversibility depends principally on the type and extent of neurological damage: peripheral nerves generally regenerate, whereas lesions of the brain and special sense organs are more often associated with permanent deficits. Taken together, these principles should be useful to identify other solvents with neurotoxic potential so that future human exposure to harmful concentrations may be prevented.

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References

1. Altenkirch H, Wagner HM, Stoltenburg-Didinger G, Steppat R. Potentiation of hexacarbon-neurotoxicity by methyl-ethyl-ketone (MEK) and other substances: Clinical and experimental aspects. *Neurobehav Toxicol Teratology* 4 (1982) 623—627.
2. Andersson A. Health dangers in industry from exposure to trichloroethylene. *Acta Med Scand* 157 (1957): suppl 323, 7—220.
3. Anger WK, Johnson BL. Chemicals affecting behavior. In: O'Donoghue J, ed. *Neurotoxicity of industrial and commercial chemicals*. CRC Press, Boca Raton, FL (in press).
4. Antti-Poika M. Prognosis of symptoms in patients with diagnosed chronic organic solvent intoxication. *Int Arch Occup Health* 51 (1982) 81—89.
5. Arlien-Søborg P, Bruhn P, Gyldensted C, Melgaard B. Chronic painters' syndrome: Chronic toxic encephalopathy in house painters. *Acta Neurol Scand* 60 (1979) 149—156.
6. Bardodej Z, Vyskocil J. Trichloroethylene metabolism and its effects on the nervous system as a means of hygienic control. *Arch Ind Health* 13 (1956) 581—592.
7. Boor JW, Hurtig HI. Persistent cerebellar ataxia after exposure to toluene. *Ann Neurol* 2 (1977) 440—442.
8. Browning E. *Toxic solvents*. Edward Arnold & Co, London 1953.
9. Bruhn P, Arlien-Søborg P, Gyldensted C, Christensen EL. Prognosis in toxic encephalopathy: A two-year follow-up study in 26 house painters with occupational encephalopathy. *Acta Neurol Scand* 64 (1981) 259—272.
10. Cassitto MG, Bertazzi PA, Camerino D, Bulgheroni C, Cirila AM, Giloli R, Graziano C, Tomasini M. Subjective and objective behavioral alterations in carbon disulfide workers. *Med Lav* 69 (1978) 144—150.
11. DiVincenzo GG, Hamilton ML, Kaplan CJ, Dedinas J. Characterization of the metabolites of methyl *n*-butyl ketone. In: Spencer PS, Schaumburg HH, ed. *Experimental and clinical neurotoxicology*. Williams and Wilkins, Baltimore, MD 1980, pp 846—855.
12. Elofsson S-A, Gamberale F, Hindmarsh 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, Widén 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.
13. Environmental Protection Agency. Health assessment document for dichloromethane (methylene chloride). Washington, DC 1982. (EPA-600/8-82-004).
14. Feldman RG. Trichloroethylene. In: Vinken PJ, Bruyn GW, ed. *Handbook of clinical neurology, intoxications of the nervous system, part 1*. North-Holland Publishing Co, Amsterdam 1979, pp 457—464.
15. Firth JB, Stuckey RE. Decomposition of trilein in closed circuit anesthesia. *Lancet* 1 (1945) 814.
16. Flodin U, Edling C, Axelsson O. Clinical studies with psychoorganic syndromes among workers with exposure to solvents. *Am J Ind Med* 5 (1984) 287—295.
17. Gerarde HW. Biochemistry of the aromatic hydrocarbons. In: Browning E, ed. *Toxicology and biochemistry of aromatic hydrocarbons*. Elsevier Publishing Co, Amsterdam 1960, pp 65—75. (Elsevier monographs on toxic agents).
18. Giloli R, Bulgheroni C, Bertazzi PA, Cirila AM, Tomasini M, Cassitto MG, Jacovone MT. Study of neurological and neurophysiological impairment in carbon disulfide workers. *Med Lav* 69 (1978) 130—143.
19. Gold JH. Chronic perchloroethylene poisoning. *Can Psychiatr Assoc J* 14 (1969) 627—630.
20. Grabski DA. Toluene sniffing producing cerebellar degeneration. *Am J Psychol* 118 (1961) 461—462.
21. Grandjean E, Munchinger R, Turrian V, Haas PA, Knoepfel H-K, Rosenmund H. Investigations into the effects of exposure to trichloroethylene in mechanical engineering. *Br J Ind Med* 12 (1955) 131—142.
22. Hänninen H. Psychological picture of manifest and latent carbon disulfide poisoning. *Br J Ind Med* 28

- (1971) 374—381.
23. 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.
24. Hane M, Axelson O, Blume J, Hogstedt C, Sundell L, Ydreborg B. Psychological function changes among house painters. *Scand J Work Environ Health* 3 (1977) 91—99.
25. Herskowitz A, Ishii N, Schaumburg HH. *n*-Hexane neuropathy: A syndrome occurring as a result of industrial exposure. *New Engl J Med* 285 (1971) 82—85.
26. Iregren A. Effects of psychological test performance on workers exposed to a single solvent (toluene) — A comparison with effects of exposure to a mixture of organic solvents. *Neurobehav Toxicol Teratology* 4 (1982) 695—701.
27. Juntunen J, Antti-Poika M, Tola S, Partanen T. Clinical prognosis of patients with diagnosed chronic solvent intoxication. *Acta Neurol Scand* 65 (1982) 488—503.
28. King MD, Day RE, Oliver JS, Lush M, Watson JM. Solvent encephalopathy. *Br Med J* 283 (1981) 663—665.
29. Knave B, Kolmodin-Hedman B, Persson HE, Goldberg JM. Chronic exposure to carbon disulfide: Effects on occupationally exposed workers with special reference to the nervous system. *Work Environ Health* 11 (1974) 49—58.
30. Knox JW, Nelson JR. Permanent encephalopathy from toluene inhalation. *New Engl J Med* 275 (1966) 1494—1496.
31. Lazar RB, Ho SU, Melen O, Daghestani AN. Multifocal central nervous system damage caused by toluene abuse. *Neurology* 33 (1983) 1337—1340.
32. Lewey WE, Alpers BJ, Belle LS, Greskoff AJ, Drabain DL, Erich WE, Frank JH, Jonas L, McDonald R, Montgomery EJ, Reinhold JG. Experimental chronic carbon disulfide poisoning in dogs, clinical, biochemical and pathological study. *J Ind Hyg* 23 (1941) 415—436.
33. Lilis R, Stanescu D, Muica N, Roventa A. Chronic effects of trichloroethylene exposure. *Med Lav* 60 (1969) 595—601.
34. Lindström K. Psychological performances of workers exposed to various solvents. *Work Environ Health* 10 (1973) 151—155.
35. Mendell JR, Saida K, Ganansia MF, Jackson DB, Weiss H, Gardier RW, Chrisman C, Allen N, Couri D, O'Neill J, Marks B, Helland L. Toxic polyneuropathy produced by methyl *n*-butyl ketone. *Science* 185 (1974) 787—789.
36. Metrick SA, Brenner RP. Abnormal brainstem auditory evoked potentials in chronic paint sniffers. *Ann Neurol* 12 (1982) 553—556.
37. Mikkelsen S. A cohort study of disability pension and death among painters with special regard to disabling presenile dementia as an occupational disease. *Scand J Soc Med* (1980): suppl 16, 34—43.
38. National Institute of Occupational Safety and Health. Criteria for a recommended standard ... Occupational exposure to refined petroleum solvents. Cincinnati, OH 1977. (US DHEW (NIOSH) publication no 77—192).
39. O'Donoghue JL, Krasavage WJ. Identification and characterization of methyl *n*-butyl ketone neurotoxicity in laboratory animals. In: Spencer PS, Schaumburg HH, ed. *Experimental and clinical neurotoxicology*. Williams and Wilkins, Baltimore, MD 1980, pp 856—862.
40. Pryor GT, Rebert CS. Hearing loss in rats caused by inhalation to toluene, xylenes and styrene. In: *Arbetskyddsverket. International conference on organic solvent toxicity*, Stockholm October 15—17, 1984. Stockholm 1984, p 75. (*Arbete och hälsa* 1984: 29) (Abstract no 315).
41. Rebert CS, Sorenson SS, Howd RA, Pryor GT. Toluene-induced hearing loss in rats evidenced by the brainstem auditory-evoked response. In: MacFarland HN, Holdsworth CE, MacGregor JA, Call RW, Kane ML, ed. *The toxicology of petroleum hydrocarbons*. American Petroleum Institute, Washington, DC 1982, pp 314—319.
42. Sagawa K. Transverse lesion of the spinal cord after accidental exposure to trichloroethylene. *Int Arch Arbeitsmed* 31 (1973) 257—264.
43. Salvini M, Binaschi S, Riva M. Evaluation of the psychophysiological functions in humans exposed to trichloroethylene. *Br J Ind Med* 28 (1971) 293—295.
44. Sasa M, Igarashi S, Miyazaki T, Miyazaki K, Nakano S, Matsudaka I. Equilibrium disorders and diffuse brain atrophy in long-term toluene sniffing. *Arch Otorhinolaryngol* 221 (1978) 163—169.
45. Satran R, Dodson V. Toluene habituation: Report of a case. *New Engl J Med* 268 (1963) 719—721.
46. Schaumburg HH, Spencer PS. Degeneration in central and peripheral nervous systems produced by *n*-hexane: An experimental study. *Brain* 99 (1976) 183—192.
47. Schaumburg HH, Spencer PS, Thomas PK. Disorders of peripheral nerves. FA Davis, Philadelphia, PA 1983.
48. Seppäläinen AM, Haltia M. Carbon disulfide. In: Spencer PS, Schaumburg HH, ed. *Experimental and clinical neurotoxicology*. Williams and Wilkins, Baltimore, MD 1980, pp 356—373.
49. Seppäläinen AM, Tolonen M. Neurotoxicity of long-term exposure to carbon disulfide in the viscose rayon industry: A neurophysiological study. *Work Environ Health* 11 (1974) 145—153.
50. Spencer PS. Experimental evaluation of selected petrochemicals for subchronic neurotoxic properties. In: MacFarland HN, Holdsworth CE, MacGregor JA, Call RW, Kane ML, ed. *Toxicology of petroleum hydrocarbons*. American Petroleum Institute, Washington, DC 1982, pp 249—260.
51. Spencer PS, Bischoff MC. Spontaneous remyelination of spinal cord plaques in rats orally treated with sodium dichloroacetate. *J Neuropathol Exp Neurol* 41 (1982) 373.
52. Spencer PS, Foster GV, Sterman AB, Horoupian D. Acetyl ethyl tetramethyl tetralin. In: Spencer PS, Schaumburg HH, ed. *Experimental and clinical neurotoxicology*. Williams and Wilkins, Baltimore, MD 1980, pp 269—308.
53. Spencer PS, Schaumburg HH. Ultrastructural studies of the dying-back process: IV Differential vulnerability of PNS and CNS fibers in experimental central-peripheral distal axonopathies. *J Neuropathol Exp Neurol* 36 (1977) 300—320.
54. Spencer PS, Schaumburg HH, Sabri MI, Veronesi B. The enlarging view of hexacarbon neurotoxicity. *CRC Crit Rev Toxicol* 3 (1980) 279—356.
55. Struwe G, Wennberg A. Psychiatric and neurological symptoms in workers occupationally exposed to organic solvents — Results of a differential epidemiological study. *Acta Psychiatr Scand Suppl* 303 (1983) 68—80.
56. Szendzikowski S, Stetkiewicz J, Wronska-Nofer T, Karasek M. Pathomorphology of the experimental lesion of the peripheral nervous system in white rats chronically exposed to carbon disulfide. In: Hausmanowa-Petrusewicz I, Jedrzejowska H, ed. *Structure and function of normal and diseased muscle and peripheral nerve*. Polish Medical Publishers, Warsaw 1974, pp 319—326.
57. Vasilescu C. Sensory and motor conduction in chronic carbon disulfide poisoning. *Eur Neurol* 14 (1976) 447—457.
58. Vigliani EC. Carbon disulfide poisoning in viscose rayon factories. *Br J Ind med* 11 (1954) 235—244.
59. Wilson RH. Toluene poisoning. *J Am Med Assoc* 123 (1943) 1106—1108.