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SOLVENT NEUROTOXICITY: A CRITICAL ASSESSMENT OF CURRENT KNOWLEDGE

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Abstract

This paper examines current information on the acute and chronic neurotoxic properties of selected industrial solvents, principally those of interest to the paint industry. While many solvents possess acute narcotizing properties, few have been shown to induce chronic disease associated with structural breakdown of nervous tissue. The latter include n-hexane and methyl n-butyl ketone, both of which produce peripheral neuropathy; toluene, a cause of brain and spinal-cord (myelopathy) abnormalities among solvent sniffers; impure trichloroethylene, an etiological agent for cranial neuropathy and possibly for myelopathy; and carbon disulfide, an agent capable of inducing psychosis and neuropathy. All except toluene have produced chronic neurotoxicity in the industrial environment. There is no evidence to suspect that prolonged exposure to toluene, at the TLV, causes irreversible nervous-system changes in worker populations.

Numerous papers from scientists and physicians in Denmark and Scandinavia claim that occupational exposure to a variety of poorly defined organic solvents for periods of 10 or more years commonly results in a self-limiting syndrome consisting of mild encephalopathy and neuropathy. Brain dysfunction is believed to accrue with exposure and to be non-progressive once exposure is discontinued. Many of these papers can be faulted either on methodological procedure or data analysis. Nevertheless, there is cause for concern that some house painters may develop neurological abnormalities after many years of occupational exposure to solvents, principally white (mineral) spirit.

Statement of Problem

Numerous papers allege that chronic occupational exposure to "organic solvents" induces irreversible changes in neurological function characterized by personality change, memory loss, intellectual decline, autonomic dysfunction (see below), and low-grade peripheral neuropathy. Many of the symptoms are of the "neurasthenic" type and include fatigue, headache, concentration difficulty, mood lability, anxiety, stomach pain, depression, dizziness, sweating, paresthesias (pins-and-needles sensation), hand tremor, and changes in sense of smell. This syndrome reportedly occurs in many groups of workers chronically exposed to solvents, including painters, jet-fuel workers, cleaners, carpenters and degreasers. Various terms have been used to describe the condition including: painter's brain, psychoorganic syndrome, organic mental syndrome, chronic toxic encephalopathy. This type of mild dementing illness is regarded as cumulative during occupational exposure and non-progressive once exposure has terminated.

Most studies on this subject have utilized epidemiological techniques to compare and contrast findings in solvent-exposed and unexposed reference groups. Methods applied have included self-administered questionnaires, psychometric tests, neurological examination, and various clinical laboratory tests to assess neural function. The minimum duration of occupational exposure to "organic solvents" required to induce "incipient psychoorganic syndrome" has been stated (in a U.S. journal) to be as short as 3 years (Flodin et al., 1984), although most reports consider that ten or more years of occupational exposure are required. One paper (Gregersen et al., 1984) claimed unconvincingly "a tendency to a dose-effect relationship" between exposure and neuropsychological deficits. Lindstrom (1980) claimed that poor visuomotor performance in various solvent-exposed workers was related to duration of exposure. Most other papers fail to address this critical issue.

Virtually all the studies on this subject have been authored by scientists and physicians from Denmark, Sweden, and Finland. In these countries, permanent neurological deficit from chronic exposure to organic solvents is a recognized occupational disability that merits early retirement and compensation. Scientists and physicians from other European and from North American countries do not recognize this entity and have been slow to take up the investigatory challenge to prove or disprove its existence. Scientists in these countries have focused their energies on understanding the chronic effects of individual solvents, whereas Scandinavian scientists hold the view that organic solvents, as a class, have chronic neurotoxic properties.

Components and Vulnerabilities of the Nervous System

Toxicologists worldwide commonly refer to nervous-system changes induced by toxic chemicals as "CNS effects." This practice appears to have developed from the observation that many solvent vapors induce acute, reversible changes in neural function (giddiness, dizziness, sleepiness etc). Regrettably, the term is sometimes applied to all types of toxicant-induced neurological dysfunction. Since solvents produce specific changes in brain, spinal cord, and/or peripheral nerves, the term "CNS effects" is inappropriate and not used here.

The nervous system may be divided anatomically into central and peripheral divisions. The peripheral nervous system (PNS) is composed of nerve cells (neurons) and their processes (axons) which conduct information between muscles, glands, sense organs and the spinal cord or brain. The PNS includes both afferent (sensory) and efferent (motor) fibers, and both type are represented in the somatic and visceral (autonomic) components of the nervous system. Somatic afferent fibers carry sensory information from skin and muscles, while visceral afferents bring impulses from the gut, glands, and various organs. On the motor side, somatic efferents innervate striated muscle, while visceral efferents supply smooth

muscle of blood vessels, glands and gut. In toxic states involving the PNS, degeneration of somatic sensory-motor fibers leads to peripheral neuropathies associated with sensory loss (eg. decreased sensitivity to vibration, touch, heat, cold or pain) and motor weakness in distal extremities, while dysfunction or breakdown of autonomic fibers may lead to abnormalities of sweating, cardiovascular changes, and gastrointestinal, urinary-tract, or genital dysfunction.

Clinical manifestations of central nervous system (CNS) damage depend largely on the site and nature of the induced functional change or structural damage. The CNS consists of those parts of the nervous system contained within the skull and vertebral column. The spinal cord receives information from afferent fibers supplying skin, muscles, and glands, sends out commands for motor function by way of efferent fibers, and communicates with higher centers in the brain. The brain is immensely complex and responsible for initiating, receiving, and integrating signals needed to maintain internal homeostasis, cognition, awareness, memory, language, personality, sexual behavior, sleep and wakefulness, locomotion, sensation, vision, audition, balance, and many other body functions. The brainstem, consisting of the midbrain, pons, and medulla oblongata, receives and processes information from skin, muscles and special sense organs (eg. inner ear) and in turn controls those muscles, as well as certain autonomic functions. The cerebellum and basal ganglia are important for modulating and coordinating muscle movement. The diencephalon, including the thalamus and hypothalamus, is a relay zone for transmitting information about sensation and movement, and also contains important control mechanisms to maintain the internal homeostasis of the body. The hypothalamus is the center which reinforces and coordinates the neural and humoral mechanisms of emotional expression. The cerebral hemispheres, capped by the cerebral cortex, are concerned with perceptual, cognitive, motor, sensory, and visual function. The optic nerves and radiations conduct visual information from the retina through the thalamus to the occipital cortex.

Compounds of Interest

The solvents of principal interest in this report include: toluene, acetone, naphtha (15-199°C), xylene, isopropyl alcohol, methyl ethyl ketone, butyl acetate, ethyl acetate. A few other solvents are considered when relevant to the problem at hand.

The exact composition of naptha is unknown. According to the NIOSH Criterion Document for Refined Petroleum Solvents (NIOSH, 1977), painters' naptha is a refined petroleum solvent boiling at 95-160°C and composed of organic compounds whose carbon chain lengths vary from C5 to C11. The chemical composition of a typical painters' naphtha would be: 55.4% paraffins (i.e. including n-hexane), 30.3% monocycloparaffins, 2.4% dicycloparaffins, 0.1% benzene, 11.7% alkyl benzenes, 0.1% indans and tetralins. Since the boiling point of the naphtha of current interest is higher than the NIOSH description, hydrocarbons with short chain lengths are likely to be poorly represented in this solvent mixture.

Mineral (white) spirits, the focus of much attention in Scandinavian reports, is a refined petroleum solvent with a boiling range of 150-200 °C consisting typically of 80-86% saturated hydrocarbons, 1% olefins and 13-19% aromatics (NIOSH, 1977).

General Principles

The literature on chronic solvent neurotoxicity may be divided into two broad categories: (a) those reports which, in sum, demonstrate unequivocal adverse neurological effects in humans and experimental animals exposed to known or estimated concentrations of more-or-less pure, single or paired compounds, and (b) other reports describing poorly defined effects on humans and/or experimental animals of one or more compounds whose identity, purity, and degree of exposure may be unknown. The first group of reports provides a solid base

from which to estimate the validity of those reports that fall into the second category and to estimate the risk to human health from occupational exposure to individual substances. The vast majority of the reports from Denmark and Scandinavia alleging irreversible neuropsychiatric disease from chronic exposure to one or more organic solvents fall into the second category.

Before embarking on a detailed analysis of the literature, it may be helpful to summarize some of the essential principles underscoring present understanding (or ignorance?) of the neurotoxic action of solvents and other chemical substances:

1. While brief exposure to high concentrations of most, if not all, solvents induce short-lasting effects on brain function, few have been shown unequivocally to exert chronic neurotoxic effects associated with breakdown of tissue. None has been proven to act by inducing an irreversible functional abnormality.

2. The acute neurotoxic properties of large doses of a solvent provide no indication of whether prolonged exposure to lower levels will lead to neurological disease.

3. Acute neurotoxic effects that do not render the brain ischemic or hypoxic are usually rapidly and fully reversible.

4. There may be no relationship between the nature and mechanism of the acute neurotoxicity of a compound and its chronic neurotoxic expression. For example, an acute neurotoxic effect of a solvent may be attributable to the parent compound, while a chronic effect may be associated with a metabolite of this compound. Both effects may coexist at one time in the same individual.

5. Acute and chronic neurotoxicities are syndromes whose temporal expression in an exposed individual is a function predominantly of the dose and duration of exposure.

6. There is specificity between chemical structure and neurotoxic effect, and neurotoxic chemicals exert similar nervous-system effects in different individuals. For example, a fixed dose of 2,5-hexanedione (the neurotoxic metabolite of n-hexane) always produces a stereotyped pattern of axonal degeneration in a particular species, whereas a closely related compound, 2,4-hexanedione, never produces such changes in the same species.

7. Experimental animal studies suggest a reasonably steep dose-response curve for the acute and chronic neurotoxicity of solvents. Thus, the majority of exposed individuals will develop neurotoxic responses when subjected to a dose and duration of exposure greater than the effective dose and duration of exposure for any one compound.

8. Certain conditions may render individuals more susceptible to the neurotoxic properties of substances. These include renal or hepatic dysfunction, metabolic conditions (eg. diabetes mellitus) associated with nervous system dysfunction, exposure to drugs (including alcohol) with neurotoxic properties or effects on solvent metabolism. In two known cases, one solvent is reported to alter the chronic neurotoxic potency of a second solvent.

9. Cessation of chronic exposure to a neurotoxic substance may be followed paradoxically by a period of intensified abnormality prior to the onset of recovery.

10. Chronic neurotoxic diseases usually are slowly and incompletely reversible, sometimes are irreversible, and rarely progressive.

Aliphatic Hydrocarbons

This subject has been reviewed by Spencer et al. (1980) and no new information has surfaced that challenges the clinical statements therein. For fuller reading and references to statements below, the reader is referred to the appended copy of this review article.

Alkanes

It is firmly established from human observation and experimental animal studies that subchronic exposure to n-hexane causes peripheral neuropathy. n-Hexane is metabolized to 2,5-hexanedione, the proximal neurotoxic metabolite. Gamma diketones of longer-chain alkanes produce an identical pattern of experimental neuropathy, although the neurotoxic potency of these ketones diminishes in proportion to the length of the carbon backbone. Since alkanes normally undergo initial metabolism by sub-terminal carbon oxidation, the possibility of forming gamma diketones from alkanes higher than C6 is minimal. Alkanes longer than C6 are therefore unlikely to produce neuropathy. In addition, pentane and hexanes other than n-hexane are unable to form gamma diketones and do not induce experimental neuropathy.

Polyneuropathy has occurred in humans occupationally exposed to solvent mixtures containing n-hexane. Initial complaints are numbness of fingers and toes that may ascend to the level of the hands and knees. Deep tendon reflexes, vibration and position sense, are only mildly impaired. Muscle weakness and atrophy subsequently affect the hands and lower legs. The disability may increase in severity for 1-4 months after exposure and then slowly regress. Recovery may be incomplete.

Severe exposure to solvents containing n-hexane has occurred among glue-sniffers. Affected individuals develop a sub-acute, distal-to-proximal progression of weakness early

in the course of the disease. Cranial-nerve deficits are rare and there is only one instance of memory loss. Autonomic dysfunction (blue-discolored hands, hyperhydrosis) may occur. Seizures, toxic delirium, cerebellar ataxia, or tremor, are not documented. Muscle weakness and autonomic dysfunction may persist after discontinuation of exposure, and mild spasticity may appear.

Ketones

Identical types of polyneuropathy have developed in individuals occupationally exposed to methyl n-butyl ketone, a substance also metabolized to 2,5-hexanedione and of higher neurotoxic potency than n-hexane. Methyl isobutyl ketone and methyl ethyl ketone are unable to induce neuropathy in experimental animals. Reports of methyl ethyl ketone producing neuropathy in humans are generally weak and unacceptable. However, there is good evidence that methyl ethyl ketone substantially increases the neuropathic potency of n-hexane or methyl n-butyl ketone. Although methyl ethyl ketone is a component of solvent mixtures implicated in the development of occupational organic mental syndrome in Scandinavia or Finland, there are no data demonstrating this effect in individuals exposed to the pure compound. Such changes were not noted in workers who developed polyneuropathy from exposure to methyl n-butyl ketone and who additionally had been exposed for many years to methyl ethyl ketone and methyl isobutyl ketone (Allen et al. 1975). Olson et al. (1981) reported behavioral changes in workers exposed to high concentrations of methyl ethyl ketone; these largely disappeared after engineering improvements resulted in lower airborne concentrations. Furthermore, there was no significant increase in frequency of neurasthenic symptoms or sleep disturbances in 95 shoe-factory workers exposed to hexanes, methyl ethyl ketone (at 25% of TLV), and ethyl acetate (Mutti et al., 1982).

Acetone is not known to be a chronic neurotoxin. Spencer et al. (1978) were unable to produce neuropathy in experimental animals and there are no reports of an organic brain syndrome in association with chronic exposure to acetone.

In summary, n-hexane and methyl n-butyl ketone are able to induce reversible peripheral neuropathy in humans and animals, and concurrent exposure to methyl ethyl ketone potentiates the neurotoxic potency of these compounds. While pathological changes occur in selected regions of the central nervous system, as well as the peripheral nerves, there is no evidence from human studies that these, or related alkanes or ketones, are capable of inducing an irreversible organic brain syndrome.

Chlorinated Hydrocarbons

Trichlorethylene (TCE) and Perchloroethylene (PCE)

Pure TCE is a useful anesthetic agent with no known irreversible nervous-system effects. Acute changes in brain function have been reported by Swedish workers (Gamberale et al., 1975; 1976). Under certain physico-chemical conditions (eg. soda lime), TCE spontaneously forms dichloroacetylene, a neurotoxin with a predilection for damaging cranial nerves, notably the trigeminal nerve (Buxton and Hayward, 1967; Hopkins, 1975). Individuals exposed to impure TCE as an anesthetic developed facial dysethesias and weakness of muscles involved in mastication. Central scotomata (blind spot) is also described. Occupational exposure to TCE has been associated with CNS (neurasthenia, anxiety, insomnia) and PNS (trigeminal neuralgia) disorders, changes in autonomic function and a high frequency of subjective complaints (Grandjean et al, 1955; Bardodej and Vskocil, 1956, Andersson, 1957; Lilis et al., 1969; Feldman et al, 1970; Salvani, 1971; Konietzko et al., 1978). These effects reportedly tend to increase in frequency with length of employment

and degree of exposure. However, there are no adequate epidemiological studies of worker populations, and available reports fail to define exposure levels adequately.

Subchronic exposure to PCE, like TCE, produces a neurasthenic syndrome with subjective complaints of dizziness, headache, nausea, and fatigue. Long-term exposures reportedly induce more serious CNS effects. Acceptable evidence in support of these claims has not been encountered.

Several recent Finnish papers report chronic neurological effects in workers exposed to TCE, PCE or mixtures thereof. Antti-Poika (1982) found that while most of the neurasthenic symptoms had reversed 3-9 years after diagnosis of chronic intoxication from TCE, PCE, PCE + TCE, or solvent mixtures, memory disturbances had deteriorated in 37%. There was no control group for the follow-up study and little confidence can be placed on an investigation that relies on grading subjective symptoms. A companion neurological study indicates that only 14 individuals in this group were exposed to TCE or PCE, 53 to solvent mixtures, and 13 to solvent mixtures + TCE or PCE. Trigeminal sensory defects (probably attributable to dichloroacetylene from TCE breakdown) were found in 15 patients initially and 18 at re-examination (Juntunen et al., 1982). A third paper described the overall prognosis in this group of workers (Antti-Poika, 1982a): 21 patients "had deteriorated," 23 "had improved," and 43 "remained unchanged." There was no significant correlation between overall prognosis and age, sex, duration and level of exposure, or the termination of exposure after diagnosis, the presence of other diseases, or the use of alcohol.

Methylene Chloride

Methylene chloride is widely used as a paint solvent (ASF, 1980) but has not attracted the attention it deserves as a possible cause of chronic CNS dysfunction. Carbon monoxide, an agent which at high doses is known to have the potential to produce a progressive dementing

illness, is a metabolite of methylene chloride. The symptoms of acute overexposure to methylene chloride include dizziness, nausea, tingling or numbness of the extremities, a sense of fullness in the head, a sense of heat, stupor or dullness, lethargy and drunkeness. Exposure to very high concentrations may lead to rapid unconsciousness and death (Torkelson and Rowe, 1981). The effects of chronic occupational exposure on brain function, if any, are unknown and uninvestigated. Since the risk of brain damage from carbon monoxide appears to be associated with the development of abnormally elevated levels of carboxyhemoglobin (Ginsberg, 1980), a priori smokers (who have elevated carboxyhemoglobin levels) should be more at risk from overexposure to methylene chloride than non-smokers.

1,1,1-Trichloroethane

While methyl chloroform is capable of inducing narcosis and anesthesia, a clinical, neurophysiological and behavioral study of female workers chronically and exclusively exposed to this agent (110-990 ppm) found no differences from a reference solvent-unexposed group (Maroni et al., 1977).

Esters

No reports have been encountered suggesting that butyl or ethyl acetate induce nervous-system damage after chronic exposure.

Aromatic Hydrocarbons

Systematic examination of the nervous system of animals exposed subchronically to benzene derivatives has not been undertaken, except in the case of toluene (see below). However,

extensive studies with one compound, a tetralin derivative (8-acetyl-1,1,4,4-tetramethyl-7-ethyl-1,2,3,4-tetralin) (AETT), have demonstrated the potential for severe damage to brain, spinal cord, and peripheral nerves following repeated skin application to rodents. Treated animals develop a syndrome consisting of hyper-irritability, back-arching and limb weakness; neuropathological examination reveals degeneration and/or pigmentary accumulation in nerve cells located in the cerebral cortex, brainstem and dorsal root ganglia (Spencer et al., 1979; Spencer, 1980).

Table 1. List of Chromogenic Aromatic Hydrocarbons+

Monocyclic	Dicyclic
Benzene	Indane
o-Xylene	Indene
o-Ethyl toluene	Tetralin
o-Diethyl benzene	Diphenyl
m-Diethylbenzene	Diphenylmethane
o-Diisopropylbenzene	1-Methylnaphthalene
Triethylbenzene	1-Ethylnaphthalene
Diethyldiisopropylbenzene	1-Ethylnaphthalene
	2-Ethylnaphthalene

+Rats receiving a single subcutaneous dose of 5 ml/kg reportedly developed blue discoloration of tissues and/or urine. Reproduced from H.W. Gerarde (1960) Toxicology and Biochemistry of Aromatic Hydrocarbons. Amsterdam, Elsevier.

The neurotoxic property of AETT appears to be related to a chromogenic property shared by several other aromatic hydrocarbons (Table I), since substitution of the 6-ethyl group by a 6-methyl results in a loss of chromogenicity and a loss of neurotoxicity. One of the agents listed in Table I, tetralin, reportedly caused excretion of green-colored urine in percutaneously exposed workers (Browning, 1953) and was singled out for comment in one of the Scandinavian reports on solvent neurotoxicity in painters (Molhave and Lager, 1976). However, tetralin has not been tested for neurotoxic properties. Certain other aromatic hydrocarbons, including benzene, diphenyl, and naphthalene, have been reported to have chronic neurotoxic potential in humans.

Xylene

Commercial xylene is a mixture of ortho-, meta- (predominately) and para-xylene, and ethyl benzene. Workers exposed to commercial xylene have experienced sleepiness, headache, irritability, fatigue, dizziness, insomnia, nausea, and indigestion (Browning, 1953; Sukhanova et al., 1969; van Oettingen, 1958). Several papers have described chronic neurological effects in workers exposed to solvent mixtures containing xylene (Lindstrom, 1973; Hanninen et al., 1976; Hane et al., 1977). No report has been found attributing development of an organic brain syndrome exclusively to chronic exposure to commercial xylene.

Toluene

INHALATION ABUSE: There is clear evidence from isolated human cases that repeated exposure to large concentrations of toluene leads to irreversible changes in the brain, spinal cord and auditory pathways. While these exposures involve individuals abusively inhaling toluene for its euphoric properties, this experience is useful for the present purpose as a yardstick with which to measure industrial experience with this agent. Toluene is a substance preferred by many inhalant users, and individuals given to this practice may

repeatedly inhale commercial products containing toluene over long periods of time. Reports of inhalation abuse with pure toluene have been few, and these have emphasized the development of cerebellar ataxia in individuals engaged in the practice for periods of one to twenty years (Wilson, 1943; Grabski, 1961; Boor and Hurtig, 1977; King et al., 1981; Lazar et al., 1983). Progressive and irreversible multifocal CNS dysfunction with unequivocal pathological changes in brain tissue also have been reported in individuals abusively inhaling toluene-based paints (Satran and Dodson, 1963; Knox and Nelson, 1966; Boor and Hurtig, 1977; Keane, 1978; Sasa et al., 1978; Streicher et al., 1981; Fornazzari et al., 1982; Metrick and Brenner, 1982; Lazar et al., 1983).

There are now sufficient reports of human toluene abuse to construct a reasonably definite picture of the natural history of the clinical manifestations. Acute intoxication is characterized by transient euphoria, exhilaration and excitement; larger doses lead to headache, fatigue, confusion, tinnitus, ataxia, and a sensation of drunkeness. Nausea, vomiting, and disordered equilibrum may occur, and unconsciousness and death have been reported. Repeated episodes of acute human intoxication were once reported in the dye and rotogravure industry, where workers often complained of headache, decreased work capacity, impaired concentration, loss of normal appetite and increased irritability. These symptoms disappeared when exposure was discontinued (Satran and Dodson, 1963).

Chronic neurological abnormalities from toluene abuse appear insidiously. Personality changes may develop before the appearance of overt signs of neurological dysfunction. Patients are described as anxious, impulsive and emotionally unstable (Satran and Dodson, 1963; Knox and Nelson, 1966; Sasa et al., 1978). There may be increased irritability and exaggerated swings of mood, and bizarre and inappropriate behavior may eventually develop (Knox and Nelson, 1966). Difficulty with memory also has been noted (Boor and Hurtig, 1977). A fast, coarse tremor of the hands is an early sign of abnormality; in the initial

stages of the diease, tremor disappears when toluene is inhaled. Eventually, tremor is persistent and may spread to involve arms, lower limbs, trunk and neck (Sasa et al. 1978). Thereafter, there is difficulty maintaining balance, progressive unsteadiness and incoordination of all four limbs, slurring of speech, bilateral hearing loss, irregular jerking movements of the eyes, difficulty reading, and mild impairment of memory and concentration (Lazar et al., 1983). Additional signs of visual loss with optic atrophy have been reported in individuals abusively inhaling mixed vapors containing toluene (Keane, 1978). Peripheral neuropathy has been seen in individuals inhaling solvent mixtures containing toluene and n-hexane, but clinical and electrophysiological evidence of peripheral neuropathy has been absent from individuals with severe and irreversible brain dysfunction from chronic inhalation of pure toluene. Thus, toluene appears unable to cause peripheral neuropathy.

Examination of individuals with chronic toluene encephalopathy reveals changes that depend on the degree of compromise suffered by the individual. The following description summarizes the findings in a "typical" patient with unequivocal brain damage after many years of toluene abuse. Physical examination is unremarkable or reveals evidence of weight loss. Serum chemistry is normal. Hand tremor, nystagmus, a titubating, wide-based ataxic gait, brisk deep tendon reflexes, Babinski responses, and signs of frontal release are evident on neurological examination. Dysmetria is prominent. Speech is slow and scanning. Audition may be normal or abnormal. Brainstem auditory evoked potentials (BAEP) reveal abnormalities in the auditory pathway in the presence of normal sensory terminal function. Visual evoked responses (VER), somatosensory evoked responses (SER) and cerebrospinal fluid (CSF) are usually normal. Electroencephalography (EEG) is normal or shows changes consistent with mild encephalopathy. Pneumoencephalography (PEG) or computer tomography (CT) demonstrate ventricular dilatation and widened cortical sulci, especially in the frontal or temporal cortex, and brainstem and/or cerebellar atrophy. Peripheral nerve

function (vibration, position, nerve conduction) is unremarkable (Kelly, 1975). Psychological tests reveal impaired cognitive functions (reasoning, judgement, logic), emotional difficulties, and defective immediate memory for language.

One individual who inhaled pure toluene at 1-3-minute intervals throughout the day for 14 years showed erratic performance at the upper end of the average range of the Wechsler Adult Intelligence Scale. He had no difficulty comprehending the tasks of spatial relations. Block designs were well performed and slight impairment of the digit-symbol subtest was mostly due to tremor, but he did well on the similarities sub-test. The psychologist believed that the tests did not conclusively suggest organic mental deterioration. The Rorschach test suggested a chronic schizophrenic process with loose associations and frequent bizarre responses accompanied by little affect (Knox and Nelson, 1966).

The cardinal clinical features of mild chronic toluene encephalopathy are changes in mentation, tremor, nystagmus, ataxia, slurred speech, high-frequency hearing loss, commonly in the presence of objective evidence of cortical, cerebellar or brainstem atrophy or dysfunction (Boor and Hurtig, 1977; Lazar et al., 1983; Kelly, 1975; Knox and Nelson, 1966; Sasa et al., 1978). Although toluene abstinence in the early stages of this disease may lead to a reversal of the tremor and ataxia, no treatment is available to reverse the frank abnormalities in brain structure and function that eventually set in.

There are no firm data on the dose or duration of toluene exposure required to induce chronic encephalopathy. Controlled studies indicate that exposure throughout the working day may lead to drowsiness and mild headache (50 ppm), fatigue, muscular weakness, confusion, paresthesias, headache and nausea (200 ppm), incoordination and mental confusion (400 ppm), extreme fatigue, mental confusion, exhilaration, dizziness, severe headache and nausea, staggering gait, insomnia and dilated pupils (600 ppm). These effects disappear

within a period of one day. Exposure to 800 ppm rapidly results in fatigue, confusion, lack of self control, with after-effects lasting for several days and consisting of severe nervousness, muscular fatigue and severe insomnia. The average concentration in blood of individuals exposed to 800 ppm is 2.23 mg/100 ml (van Oettingen, 1958). Patients with chronic toluene encephalopathy routinely experience these symptoms and may, on occasion, develop unconsciousness. Transient blood levels of 6.5 mg/100 ml have been recorded in glue sniffers. It is reasonable to assume, therefore, that chronic toluene encephalopathy develops in individuals repeatedly exposed to concentrations significantly greater than 800 ppm for periods of between 1 and 20 years.

ANIMAL STUDIES: There are few relevant data from experimental animal studies, and there is no animal model of the chronic brain damage reported in individuals abusively inhaling large concentrations of toluene for prolonged periods. However, cortical and cerebellar degeneration have been reported in dogs after 4-6 weeks of intermittent intravenous administration of toluene, where blood levels were estimated to reach peak values of 10 mg/100 ml (Knox and Nelson, 1966). Rats exposed to 100 or 1500 ppm of pure toluene, 6/h day, 5d/week, for periods up to 6 months, failed to disclose any neuropathological changes in CNS or PNS tissues, including the cerebellum, brainstem and optic nerve. Rats exposed to 900 or 1400 ppm 14h/day, 7d/week for 14 weeks also failed to develop neuropathy and showed no changes in VER, SER or BSER. High-frequency hearing loss was noted after only 5 weeks of exposure to 1200 ppm or 1400 ppm: this was attributed to cochlear dysfunction rather than the central conduction pathology found in humans with chronic toluene encephalopathy (Rebert et al., 1982). Objectively measured changes in auditory function occur in rats exposed to 1400 ppm of toluene for 5 weeks, but detectable structural damage to cerebellum or brainstem has failed to appear for periods of equivalent exposure lasting 6 months. Since the pharmacodynamics, distribution and bioavailability of toluene and its metabolites are barely investigated, there is no basis for comparing the

effects on animals and humans of comparable exposures to toluene. Experiments are needed to determine the effects on neural structure and function of prolonged exposure (years) to high concentrations of toluene (in excess of 1500 ppm) in a sensitive species (dog?) and to correlate the development of these effects with levels of toluene and its metabolites in blood and urine.

OCCUPATIONAL EXPOSURES: Four papers from Sweden describe the results of two studies of 37 rotogravure printers occupationally exposed almost exclusively to toluene (91-97%) at an ambient concentration of between 50-150 ppm, with excursions to 1000 ppm (Elofsson et al., 1980; Iregren, 1982; Struwe and Wennberg, 1981, 1983). The printers had been the subjects of a substantial amount of media publicity about the possible health hazards of organic solvent exposure. Their mean age was 38.4 $\pm$ 12 years, with mean exposures of 16.3 (range 3-32) years. Controls consisted of 37 workers from an electrical plant without solvent exposure and matched for age. Results of a self-administered questionnaire designed to elicit symptoms of tiredness, dreaming, fatigue, memory failure, anxiety, headache, tinnitus, etc., failed to distinguish the printers from controls. Psychometric study failed to reveal any differences between the printers and controls, with the exception of a prolonged reaction time in the printers that was judged to be an acute effect of toluene. There were no statistically significant differences between painters and controls on examination by EEG, VER, nerve conduction or for vibratory sensation.

SUMMARY: There is strong evidence that chronic abuse of concentrations of toluene substantially in excess of 800 ppm leads after 1-20 years to irreversible brain damage manifest initially as changes in personality and cerebellar dysfunction. Evidence of chronic toluene encephalopathy from occupational exposure to this compound is lacking, although one study reported cerebellar defects that increased in severity with time of occupational exposure to organic solvents containing up 20% aromatic hydrocarbons (mostly xylene and

toluene) (Juntunen et al., 1982). Individuals occupationally exposed for mean periods of 18 years to concentrations of toluene approximating the U.S. Threshold Limit Value (100 ppm) show no deficits in brain or nerve function when assessed by Swedish scientists who have repeatedly reported nervous-system dysfunction in workers chronically exposed to mixed solvents.

Styrene

Psychological decrements have been reported in workers exposed to styrene with improvement occurring after 35 exposure-free days (Kjellberg et al., 1979). Reports of polyneuropathy in humans occupationally exposed to styrene have not been confirmed by animal studies (Politis et al., 1980). Vestibulo-oculomotor disturbances have been demonstrated in subjects acutely exposed to styrene under controlled circumstances There are no reports of solvent abusers using styrene, nor is chronic styrene intoxication known to produce the cerebellar and corticospinal deficits found in chronic toluene abusers.

Mixed Solvents

The vast majority of solvent-toxicity studies emanating from Sweden, Finland, and Denmark, report neurological changes in individuals occupationally exposed to various solvent mixtures.

Stockholm Automobile Spray Painters

These studies used a questionnaire, and psychometric and electrophysiologic tests to examine a group of 74 spray painters "severely exposed" to white spirit (85 ppm), toluene (39 ppm), methylene chloride (28 ppm), MEK (26 ppm), ethanol (19 ppm), xylene (14 ppm), styrene (7 ppm), MBK (5 ppm), trichlorethylene (5 ppm) and minor concentrations of some

other compounds. Mean age was 38.4 +12.4 years, with mean exposures of 11.8 (range 1-38 years) (Elofsson et al., 1980; Iregren, 1982; Struwe and Wennberg, 1981, 1983). Individuals were not exposed during the 1.5 days prior to testing. No differences from controls were found on examination by EEG, computer tomography or VER. Psychometric measurements showed small, statistically significant differences in reaction time, manual dexterity, perceptual speed, and short-term memory, functions that might be impaired as a consequence of acute exposure. No dose-response was demonstrated and there is no justification for a statement in a later paper referring to these results as demonstrative of "an impairment of mental functions indicative of an organic brain lesion" (Struwe and Wennberg, 1983). No differences were found from controls on examination by EEG or VER. Nerve conduction was reportedly slightly decreased in sural nerves and this was interpreted as evidence of axonal neuropathy (Elofsson et al., 1980). However, detailed morphometric study of sural nerve biopsies by an independent and highly respected group of Swedish anatomists failed to find any differences attributable to solvent exposure between controls (N = 11) and four "massively exposed" solvent workers with sural nerve conduction velocities ranging from 33-48 m/sec (controls 41-48 m/sec) (Berthold et al., 1983). In conclusion, these papers fail to demonstrate any evidence of organic nervous-system dysfunction in the spray painters. Furthermore, there was no convincing evidence of peripheral neuropathy despite the workers' chronic exposure to low levels of methyl ethyl ketone and methyl n-butyl ketone.

Helsinki Automobile Spray Painters

Several papers compare findings from 102 male painters (mean age 35 years, range 20-65; mean exposure 14.8 years, range 1-40) exposed to mixed solvents with 54 age-matched (± 2 years) engineers with no history of solvent exposure (Hanninen et al., 1976; Seppalainen et al., 1978; Husman, 1980; Husman and Karli, 1980). At the time of the study, painters were exposed to toluene (mean 33 ppm, range 5-249 ppm), butyl acetate (7; 1-128), xylene (6; 1-

36), white spirit (5; 1-150), acetone (3; 1-25), ethanol (3; 1-27), isopropanol (3; 1-85), ethyl acetate (3; 1-14) and methyl isobutyl ketone (2; 1-39). Health histories were collected with a questionnaire, and subjects were given clinical, psychological, neuroophthalmological and neurological examinations, together with a number of laboratory tests (Seppalainen et al., 1978). Distal vibratory sense was diminished more in the lower limbs than upper limbs of spray painters vs controls, although the former group included some individuals aged 55-65 in whom diminished vibratory sensation would be maximal. There was no evidence of increased peripheral motor abnormalities. Nerve conduction velocities in peroneal, tibial and sural nerves were identical in the two groups; distal motor latencies in peroneal and tibial nerves were statistically similar. Objective evidence of polyneuropathy was therefore absent and none of the solvents involved is known to cause this type of neurological disease. Cerebellar and extrapyramidal findings were rare and similar in frequency between painters and controls (Husman and Karli, 1980).

The validity of the results of the self-administered questionnaire are open to question since some respondants would likely have been aware of the publicity given to neurotoxicity among solvent workers. However, taken at face value, spray painters more frequently reported tiredness and difficulties with concentration and memory at the end of the workday, but not in the morning. Nausea, vomiting, dizziness, and absent-mindedness also were more common among the painters (Husman and Karli, 1980). These symptoms were judged to be acute effects of solvent exposure and are therefore unrelated to chronic, irreversible brain damage. Psychoorganic syndrome was reported in 13 (9 slight, 2 clear-cut) exposed subjects and 2 (slight) controls. EEG showed a high level of abnormalities in both groups with no significant differences between groups and no correlation with head injury (Seppalainen et al., 1978). Taken together, these data provide insufficient evidence of an organic brain syndrome attributable to exposure to solvents. In particular, there is no evidence of abnormalities associated with chronic exposure to toluene.

Danish and Swedish House Painters

Four papers report neuropsychiatric disorders among house painters in Denmark and Sweden (Hane et al., 1977; Arlien-Soborg et al., 1979; 1981?; Bruhn et al., 1981; Lindstrom and Wickstrom, 1983).

The Swedish studies were performed on a group of house painters/wallpaper hangers, aged 25-60 years, with estimated exposures to "several hundred parts per million of hydrocarbon solvents" for 4-42 "painter years." Referents came from various groups of workers not exposed to solvents. Approximately 50% of each group had performed similarly in military intelligence tests performed at 20 years of age. Interviews revealed eczema and experiences of impaired memory more frequently among painters than referents. Psychological tests on painters suggested significantly lower mean performances on visual/logical and psychomotor tests. Although these tests were performed "more than 15h after last exposure," there is no evidence from these data that the painters had developed a chronic psychoorganic syndrome as claimed by the authors (Hane et al., 1977). The study also suffers from a failure to present an analysis of the solvents to which the painters were exposed, to exclude the possibility of residual acute effects from solvent exposure, and to exclude alcoholics and other individuals with metabolic diseases.

Lindstrom and Wickstrom (1983) reported altered sense of smell and forgetfulness in 219 maintenance house painters exposed on an average to 40 ppm of white spirit (see below). A control group of concrete workers unexposed to solvents performed better on psychological tests measuring reaction time, short-term memory and "sensory and motor speed." Testing was performed too soon (20 hours) after exposure to rule out acute toxic effects. No abnormalities of EEG or nerve conduction velocity were found in 72 of these house painters relative to the control group (Seppalainen and Lindstrom, 1981).

Gregersen et al. (1984) included 10 painters exposed to white spirit (up to 250 ppm) among 55 workers exposed to various solvents, including perchlorethylene, styrene, toluene, petrol, kerosene, methyl ethyl ketone, ethyl acetate, butyl acetate and glycols). Acetone was used to wash the hands of some workers. Controls consisted of 33 solvent-unexposed electricians and warehousemen. Examination took place 40 hours after last exposure. Psychological tests suggested slight differences between groups. Peripheral neuropathy did not occur more frequently.

Danish studies focused on 50 male house painters, mean age 47 years (range 24-63 years), with a mean exposure time to organic solvents (principally white spirit) for 8-50 (mean: 27) years. The exposure-free period prior to examination was 5 day to 5 years, sufficient time to rule out acute effects. Symptoms consisted of asthenia, anxiety, depressive complaints, headache, dizziness, fatigue, emotional complaints and disorders of the autonomic nervous system (bursts of perspiration, palpitation, diarrhea, sexual impotence). Unspecified EEG changes were found in 18%, rapid intermittent tremor in 6, clinical signs of peripheral neuropathy in 9 and electrophysiological evidence of neuropathy in 3. The type of neuropathy and nerves tested were not specified. Eighteen of 42 subjects had unspecified otological abnormalities and 12 had a reduced caloric vestibular reaction. PEG analysis showed abnormally widened cortical sulci in all 12 tested. CT scan of 38 subjects showed 13 with widened (6.6 mm) hemispheric sulci, 5 with ventricular enlargement and one with "combined central and cortical atrophy." Thirty-nine of 50 were judged to be intellectually impaired, with memory most often affected (Arlien-Soborg et al., 1979). Twenty-six of these patients who had cerebral atrophy or intellectual impairment were followed up 2 years later. Generally the condition was unchanged. Headache, dizziness, and irritability had diminished in some, while the degree of brain atrophy and neuropathy were unchanged (Bruhn et al., 1981). The original and follow-up studies both lack a matched control group. No attempt was made to relate duration of exposure to degree of impairment.

These papers were followed by a study examining cerebral blood flow (CBF) in 11 control and 9 house painters exposed to organic solvents for a mean of 22 years with an exposure-free interval prior to examination of 27 days to 9 years (Arlien-Soborg et al., 1981?). House painters showed mild intellectual impairment: CT-scan was normal in 6 and showed slight cortical atrophy in 3, while the neurological exam was normal. CBF was reduced significantly by 19%. Risberg and Hagstadius (1983) also reported small decrements (4%) in cerebral blood flow of 50 male paint-factory workers vs. 50 referent workers from a sugar refinery. Largest differences in blood flow were seen in frontotemporal areas, especially of individuals with higher exposure. The significance of these small differences in blood flow of solvent-exposed workers is unknown.

Social scientists in Denmark have compared the incidence of disability pensioning and mortality among a cohort of 2601 male painters and 1790 male bricklayers. Total mortality in painters was comparable in painters to the general population of the area (Copenhagen). There were no significant differences with respect to cancer, diseases of the respiratory system, cirrhosis, accidents or suicide. However, observed cases of dementing illness among painters was approximately 2-3 times higher than in bricklayers or in Copenhagen males (Mikkelsen, 1980). Another study of cabinet workers exposed to solvents from lacquers and glues similarly showed a high incidence of neuropsychiatric disease among solvent-exposed relative to less-exposed (controls) disability pensioners. No "diseases of the nervous system or sense organs" were found in control groups of ages 30-44, 45-59, and 60+ years, whereas 17, 46, and 30 individual solvent workers respectively were found in those groups. By contrast, incidence of cancer (solvent workers: 1, 1, and 6 vs. controls: 2, 15, 20), diseases of heart and circulatory system (1, 1, 6 vs. 2, 15, 20), respiratory system (0, 1, 0 vs. 0, 5, 8), and musculo-skeletal system (0, 3, 1 vs. 5, 17, 13) was not greater in solvent-exposed workers than controls (Olsen and Sabroe, 1980). In the opinion of these authors, "a signiifcantly high risk of obtaining a disability pension on neuropsychiatric ground(s) is seen

among union members with more than 4000 hours of exposure to solvents. The relative risk is higher for the group of individuals exposed to solvents indoors as compared to the relative risk of ... combined indoor plus outdoor exposure..."

SUMMARY: Despite several shortcomings, these papers suggest the possible existence of chronic neurological abnormalities in house painters. Neuropsychiatric changes reportedly develop after 10-30 years of exposure and appear not to progress after exposure is terminated. The lack of progression, prominence of headache among the clinical symptoms, and onset at a young age, distinguishes the syndrome from other types of organic dementias (Alzheimer and Pick) which are characterized by specific neuropathologic changes and rapid deterioration of personality and cognition leading to death within 5-10 years. No neuropathological studies of painters considered to suffer from organic mental syndrome have been reported.

Neurological abnormalities in Danish and Swedish house painters are commonly attributed to chronic occupational exposure to white spirit. This appears to be equivalent to "mineral spirits," a clear, water-white, water-insoluble, refined petroleum solvent with a pleasant, sweet odor and composed of 80-86% saturated hydrocarbons (predominantly C9-C12), 1% olefins and 13-19% aromatics. Other properties include: molecular weight: 144-169, specific gravity: 0.77-0.81, vapor pressure: 0.8 mm Hg at 20°C, flashpoint (closed): 30.2-40.5°C (NIOSH, 1977). Quantitative and qualitative analyses of this material have not been encountered, and the effects of chronic exposure to experimental animals have yet to be studied. Research efforts should be mounted to identify and test in animals the specific chemical constituents of white spirit, with emphasis placed on any components listed in Table 1.

Other Studies

Numerous other studies have appeared from Scandinavia and Finland describing neurological and psychiatric changes in workers exposed to mixed organic solvents. Some of the early papers deal with carbon disulfide, an agent that unquestionably induces neurological and psychiatric disease in humans (Seppalainen and Haltia, 1980). One study compared 50 subjects with carbon disulfide poisoning with 168 workers exposed to trichlorethylene, tetrachlorethylene, toluene, xylene, and their mixtures. Psychological testing revealed some deficits in the solvent-exposed workers and larger deficits in those exposed to carbon disulfide (Lindstrom, 1973). Neurological abnormalities (psychomotor and personality changes, cerebellar findings and peripheral neuropathy) were reported in a retrospective study of 37 patients variously exposed to carbon disulfide, trichlorethylene, styrene, thinner, toluene, methanol, and diphenyl, but no attempt was made to correlate specific chemical exposure with effect (Juntunen et al., 1980). An earlier report by Seppalainen et al. (1980) describing EEG changes in a majority of such workers was not confirmed. Yet another study from the same group of workers reported an improvement in EEGs in most workers 3-9 years later (Seppalainen and Antti-Poika, 1983). This and other papers demonstrate that electroencephalography is not a reliable technique for the detection and analysis of brain dysfunction among solvent workers.

Other studies from Sweden have reported neurasthenic changes without memory loss in workers occupationally exposed to jet fuel, a hydrocarbon mixture composed of 87.5 saturated hydrocarbons and 12% aromatics (Knave et al., 1978, 1979; Struwe et al., 1983). In the more recent study, 7 of 30 subjects exposed for 4-32 years at a jet fuel factory had undergone personality changes and were judged to suffer from mild organic brain syndrome.

CONCLUDING REMARKS

General Comments

1. Many of the studies are fragmented into several papers spanning several years, thereby making it difficult for the reader to assess the overall findings.

2. There is a tendency to misquote published references describing chronic neurotoxic properties of selected solvents to support the contention that organic solvents generally produce such adverse health effects.

3. The practice of comparing grouped scores of various tests has dubious validity. Consider the following hypothetical example in which it is assumed that painters have a higher frequency than carpenters of carpal tunnel syndrome in their dominant hand from years of daily brushwork. This abnormalitiy would be detected upon electrodiagnostic studies of the median nerve. If these scores were grouped together with other random positive electrodiagnostic findings from painters and carpenters, the data would demonstrate that painters have a tendency toward peripheral neuropathy. The uncritical observer might then incorrectly ascribe the painter's tendency toward neuropathy to solvent exposure and cite evidence in support of this contention from published studies demonstrating that (certain) organic solvents cause neuropathy.

4. Some papers compare and contrast findings between control and exposed groups, the latter representing a heterogenous collection of exposure histories both with respect to duration and type of solvent exposure. A few studies fail to include a control group.

5. While most papers carefully cite data and examine their statistical validity, there is an unfortunate lack of discrimination of significant from non-significant data when the findings are discussed. Critical writing is even less apparent in the abstract, that part of the paper which frequently enters data bases.

Conclusion

Papers from Danish, Swedish and Finnish laboratories, describing CNS effects among solvent-exposed workers, fail to recognize the relationship between chemical substance, exposure level, and specific biological effect. There is little concern given to the distinction between the acute, reversible effects on brain function generally associated with hydrocarbon solvents and the reversible or irreversible structural damage from exposure to specific dose ranges of selected agents. Contrary to the position of most U.S. neurotoxicologists, the Danish and Scandinavian investigators appear to adopt the view that since hydrocarbon solvents are acutely active CNS depressants, they are therefore likely to be chronic neurotoxins. Their position historically is traceable to experience with carbon disulfide, an agent that indeed possesses acute and chronic neurotoxic properties.

At the present time, few solvents have been shown to possess chronic neurotoxic properties. In addition to carbon disulfide, the list includes n-hexane, methyl n-butyl ketone, toluene, and impure trichloroethylene (containing dichoroacetylene). With the exception of toluene, all these agents have caused workers to develop chronic neurological dysfunction associated with degeneration of nervous tissue. Chronic neurotoxicity from toluene overexposure has been found in individuals who abusively inhale the pure compound, or mixtures containing toluene; there is no evidence to suggest that toluene is a chronic neurotoxin at levels encountered in the occupational setting. Experience with these proven neurotoxins has demonstrated that individual substances produces specific clinical and neuropathological

changes: peripheral neuropathy in the case of n-hexane and methyl n-butyl ketone, cranial neuropathies and myelopathy from impure trichloroethylene, and cerebellar, corticospinal and auditory changes from gross overexposure to toluene. None of these agents is known to produce the clinical picture of organic mental syndrome described by the Danish and Scandinavian investigators.

There is no convincing evidence that a chronic, irreversible organic mental syndrome has occurred among spray painters in Stockholm or Helsinki, or among workers chronically exposed to jet fuel or other mixed solvents. The argument that the nervous system of these workers has been adversely affected is often based on the heroic use of statistics to manipulate grouped data obtained by interviews, questionnaires and psychometric tests that have dubious reliability. However, sufficient solid data are unavailable to refute the claims of the large number of Scandinavian workers that have published on this subject.

There is cause for concern that Danish and Swedish house painters may have developed neurological dysfunction associated with irreversible structural and functional changes of the nervous system. Neuropsychiatric abnormalities reportedly appear after 10-30 years of exposure and do not progress once exposure has terminated. While some of these studies use techniques of questionable reliability, the demonstration with the aid of objective clinical tests of pathophysiological changes in the brains of numerous painters cannot be ignored. The absence of dose-response data, while regrettable, does not invalidate these findings. Efforts should be directed toward the study of post-mortem material to verify and characterize the reported changes.

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