A Review of Recent Research on Health Effects of Human Occupational Exposure to Organic Solvents

A Critical Review

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The health impact of workplace solvent exposure remains an issue of substantial interest and concern to occupational health professionals. As a result of research performed in the 1970s and 1980s, policies and programs were developed throughout the world to control excessive exposure to solvents. To an extent, these programs have been responsible for reduction of the occurrence of solvent-associated encephalopathy and other health effects. In this review of research performed since 1985, particular attention is given to issues of reversibility of neurotoxicity following exposure cessation. Furthermore, health effects involving other organ systems, particularly reproductive, renal, and hepatic disorders, are discussed. Future research directions are discussed. Finally, the practical implications of these recent research findings are described with a focus on the management of prevention programs at the work site.

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In 1985, two important international conferences were held at which the relevant literature on solvent-related effects on the nervous system was reviewed.[1,2] Health effects on other organ systems received limited attention at those conferences. Since 1985, numerous studies have been performed in an attempt to clarify the issues further.[3] This review attempts to summarize these studies.

In each section, a brief synopsis of the most important recent studies is provided, followed by an assessment of the significance of the aggregate findings in a research area. The review evaluates the need for further research and describes the practical implications of the research for control of solvent neurotoxicity in the workplace.

The Nervous System

The Central Nervous System

Neurobehavioral Effects. Cross-sectional studies. In a report prepared for a 1985 World Health Organization working group meeting, Roberta White and I summarized the existing literature on neurobehavioral testing in solvent-exposed populations.[4] In the studies we reviewed, differences between exposed and unexposed were most commonly seen on tests of psychomotor function and short-term memory. Studies published since then show a similar pattern (Table 1). In particular, performance on tests of memory function, particularly short-term memory ability, was poorer in solvent-exposed workers. In one pop-

TABLE 1
Recent Neurobehavioral Studies

Study	Exposed Group (N)	Visual Performance Motor Deficit	Memory Deficit	Behavioral Symptoms
Hanninen et al (1991)[7]	Twins (28)	+	+	−
Moen et al (1990)[8]	Seamen (85)		+	
Morrow et al (1990)[17]	Clinic patients (32)	+	+	+
Bleecker et al (1991)[5]	Paint factory workers (187)	+	+	−
Bolla et al (1990)[9]				
Parkinson (1990)[92]	Electronics plant workers (140)	−	−	+
Maizlish et al (1987)[12]	Spray painters (124)	−	+	−
Maizlish (1985)[94]				
van Vliet et al (1989)[11]	Solvent-exposed (379)			+
Fidler et al (1987)[16]	Painters (101)			+
Cherry (1985)[93]	Painters (44)	+	+	+
	Toluene-exposed (52)			
Baker et al (1988)[13]	Painters (186)	+	+	+
Spurgeon et al (1992)[6]	Painters (90)	+	+	
	Solvent-exposed (144)			

+, Exposure-related effect seen; −, exposure-related effect not seen.

ulation studied by Bleecker and colleagues,[5] deficits in performance on memory tests were observed in groups without evidence of behavioral symptoms of the type seen with solvent toxicity.

Because each study used different neurobehavioral tests, comparison of results between studies on the actual tests is difficult. However, some similarities can be observed (Table 2). Performance on two tests of short-term memory function (ie, associate learning tasks and tests of memory span) has been reduced consistently in solvent-exposed workers. Psychomotor function, as measured by the digit-symbol substitution test, was reduced in exposed workers in two recent studies, and in other studies before 1985. The block design test, evaluating visuospatial ability, also showed differences between exposed and unexposed in two recent studies.

Only a few studies attempted to develop exposure models and to compare exposure estimates with test performance. Such comparisons involve, at times, the use of statistical techniques to make the exposure-response comparison while controlling for the confounding effects of age, etc. Spurgeon et al[6] have recently completed studies of two solvent-exposed populations: brush painters (n = 90) and a heterogeneous group of solvent-exposed workers (n = 144). They observed decrements on performance on tests of psychomotor function (ie, symbol-digit substitution) and short-term memory (ie, paired associate learning) that were correlated with indices of exposure derived from work history. Those with greater than 10 years of exposure showed performance decrements particularly on memory tests. The results obtained from the two separate populations were strikingly similar.

TABLE 2
Tests on Which Solvent-Exposed Workers Performed Poorly Relative to Unexposed Workers

Study	Test	Function Tested
Hanninen et al (1991)[7]	Associate learning	Short-term memory
	Digit span	Short-term memory
	Block design	Visuospatial ability
Moen et al (1990)[8]	Memory span	Short-term memory
	Raven's matrices	Visual abstraction
Morrow et al (1990)[17]	Associate learning	Short-term memory
	Visual reproduction	Memory
	Block design	Visuospatial ability
	Pegboard	Psychomotor dexterity
Bleecker et al (1991)[5]	Digit symbol	Attention
	Serial digit learning	Short-term memory
	Reaction time	Psychomotor speed
	Trails	Attention
Maizlish et al (1987)[12]	Memory span	Short-term memory
Baker et al (1988)[13]	Symbol digit	Attention
	Reaction time	Speed
	Pattern memory	Short-term memory

In the Hanninen et al[7] Finnish report of pairs of monozygotic twins with discordant solvent exposure histories, the investigators divided their exposed population into moderate and low exposure groups. Those with moderate exposure showed greater performance decrements when compared with their twin than did those with low solvent exposure.

Moen et al[8] used an exposure index that combined intensity of exposure and duration of exposure in the 85 seamen whom they studied. This index was used in a multivariate regression model relating exposure to effect while controlling for relevant confounding factors. Performance on two tests, evaluating visual abstraction ability and memory span, showed statistically significant negative correlations with the exposure index.

In studying 187 workers in two paint manufacturing plants, Bleecker and colleagues[5,9] modelled exposure using personal breathing zone sampling results obtained over a 13- to 15-year period. The results were combined to form a lifetime-weighted average exposure estimate that was used in regression analyses. Test performance was negatively correlated with exposure on four tests (digit-symbol substitution, serial digit learning, reaction time, and trail making [A and B]) after controlling for relevant confounding factors.

Ng et al[10] observed increased neurobehavioral symptoms and reduced test performance in Chinese printing and paint workers. Increased reports of fatigue, irritability, depression, poor memory, and sleep disturbances were noted. Reduced psychomotor and memory test performance were also observed.

van Vliet et al[11] developed two exposure indices in studying 379 exposed Dutch workers: a "painters index" based on the work practices of painters in the study and a "general exposure index" for all exposed study participants. This study did not use neurobehavioral testing; a symptom questionnaire was used to assess effects of exposure. The painters index and the general exposure index were correlated with a composite score for "prenarcotic symptoms."

Maizlish et al[12] developed an exposure index based on airborne exposure measurements at the time of testing, duration of employment, and relative toxicity of quantified solvents. Test performance decrements were not correlated with this exposure index. In a study of 186 construction painters reported by Baker et al,[13] correlations between performance on various neurobehavioral tests and solvent exposure indices were observed. Disruption in mood was correlated with indices of exposure to solvents. Impaired performance on certain tests of psychomotor function also was observed to correlate with exposure intensity. Symptoms of forgetfulness, disorientation, dysphoria, lassitude, and difficulty falling asleep were noted with increased frequency by those more heavily exposed.

In 1988, Gade et al[14] performed a reanalysis of neurobehavioral test data in 20 workers previously diagnosed as having solvent encephalopathy and compared their results with 20 matched control subjects. Extensive neurobehavioral testing had been performed between 1980 and 1983; using these data, statistical analyses were performed and led the authors to conclude that the workers previously diagnosed as having solvent-associated encephalopathy had no evidence of significant neurobehavioral impairment. In this report, Gade et al[14] used statistical techniques to adjust for the presumed confounding effects of age, education, and verbal intelligence. These statistical techniques deserve particular attention because the conclusions rest heavily on the validity of the approach taken.

Controlling for the effects of age and education is common and usually appropriate in studies that use neurobehavioral tests as an outcome measure because age and education are correlated with performance on many neurobehavioral tests. However, in this study, because age and education were factors on which matching was based, the exposed and control groups were virtually identical with respect to age and education; further statistical adjustment for these two factors would seem to be unnecessary.

Adjusting for verbal intelligence differences was justified by the authors (and by others performing similar research) to address possible "premorbid" noncomparability of intellectual functioning. This adjustment was accomplished using the results on four tests (an adult reading test and the information, similarities, and vocabulary subtests of the Wechsler Adult Intelligence Scale). The assumptions underlying this procedure are that test performance on these four tests is an accurate and unbiased indicator of premorbid function in all areas of neurobehavioral function evaluated in the study and, most importantly, that test performance is not adversely effected by chronic solvent exposure. Because these assumptions have been tested inadequately in other studies and because the data of Gade et al[14] show decrements in neurobehavioral performance in tests of memory span and visuomotor speed before adjustment for verbal intelligence test performance, the significance of this study reanalysis is unclear.

Mikkelsen et al,[15] in an extensive analysis of 85 painters and 85 bricklayers, noted changes in neurobehavioral function in relationship to solvent exposure. Cerebral atrophy also was noted to be increased in relation to the history of solvent exposure. The authors observed little risk of organic brain damage in persons with fewer than 13 years of exposure to the equivalent of a time-weighted average of 40 ppm of white spirit.

In summary, these 16 studies, involving more than 1000 exposed workers in 6 different countries, on 3 continents, yield results that are reasonably consistent among themselves and with studies published before 1985. In these studies, solvent-exposed workers demonstrate decrements in short-term memory and psychomotor function. This decrement was not related to various potential confounding factors. There was, in most studies, a "dose-response relationship," such that an increased level of cumulative exposure was associated with performance decrements. The types of neurobehavioral deficits are similar to those seen in heavily exposed workers and in per-

sons with pronounced neurobehavioral dysfunction due to solvent abuse.

Some studies have focused exclusively on symptoms related to solvent exposure. A study of industrial spray painters by Fidler et al[16] showed multiple correlations between indices of exposure drawn from work history questionnaires and reports of various neurotoxic symptoms in currently employed painters (eg, dizziness, fatigue, and acute lightheadedness at work). Two other similar studies by Maizlish et al[12] and Bolla et al[9] failed to find substantial correlations between cumulative exposure indices and current symptoms. In these two studies, workers were employed in manufacturing facilities where measured exposure levels were rather low (with the exception of plant 4 in the Maizlish study) in relation to existing permissible exposure limits. Chronic symptoms consistent with prior reports of solvent toxicity were reported in a study of 32 clinic patients reported by Morrow et al.[17]

From these symptom studies, there is little convincing evidence that persistent chronic symptoms are observed in currently employed workers if they work where exposures are controlled below the permissible exposure limits. Studies reporting symptoms in exposed workers are apparently either documenting persistent symptoms developed from high exposures in the past or among workers (eg, construction painters) who are employed in situations with inadequate current exposure controls.

Although epidemiologic studies, particularly cross-sectional ones, have limits in assessing causality, criteria have been developed by which studies can be evaluated in this regard.[18] Three important criteria are (1) consistency of findings, (2) biological plausibility, and (3) presence of a dose-response relationship. The studies reviewed have demonstrated consistent results, as mentioned above. Although biologic models for solvent neurotoxicity are limited, the findings in these studies are consistent with a diffuse toxic encephalopathy that preferentially effects certain brain structures.[19] Finally, dose-response relationships were observed in most studies. Therefore, these cross-sectional studies, viewed in the aggregate, support the view that chronic solvent exposure causes impairment of neurobehavioral function.

Follow-up studies using neurobehavioral methods. Five follow-up studies (Table 3) have been performed since 1985. These studies are extremely important in evaluating the long-term significance of solvent-associated changes in neurobehavioral function. Orbaek and Lindgren[20] reported on follow-up studies of 32 men diagnosed as having chronic toxic encephalopathy 21 to 88 months previously. Symptoms improved considerably in these workers who had been removed from exposure at the time of diagnosis. Neurobehavioral testing showed deterioration in test performance on a paired associate learning task and in simple reaction time. Most neurobehavioral test results were unchanged from initial testing at time of diagnosis.

Gregersen[21] reported on follow-up of a cohort of solvent-exposed workers tested 5 and 10 years after initial examination. Exposure continued for most of the group during the interval but airborne concentrations of solvents were reduced considerably over the follow-up period. Both exposed and unexposed workers were followed over the 10-year interval. Symptoms, particularly complaints of memory disorders and impairment in concentration, improved over the period. In some workers for whom exposure ceased, symptoms persisted with a frequency greater than in the control group.

In a separate study,[22] 21 painters diagnosed as having solvent-induced chronic toxic encephalopathy were evaluated 5 years after original diagnosis. All were removed from exposure to solvents. Symptoms improved considerably. Neurobehavioral testing showed impairment in memory, attention, and abstraction ability. Social follow-up revealed that those who were able to return to work in another

TABLE 3
Follow-Up Studies

Study	Subjects (N)	Follow-up Interval, y	Results
Orbaek et al (1988)[20]	Chronic toxic encephalopathy (32)	2–7	Symptoms: better Tests: some worse, others unchanged
Gregersen (1988)[21]	Solvent-exposed (59, 53)	5.5 and 10.6	Symptoms: better
Gregersen et al (1987)[22]	Chronic toxic encephalopathy (21)	5	Symptoms: better Tests: unchanged
Edling et al (1990)[23]	Symptomatic only (65) Chronic toxic encephalopathy (46)	6.8 (mean) 6.7 (mean)	Symptoms: better Symptoms: unchanged
Morrow et al (1991)[24]	Toxic encephalopathy		Tests: some improved

job were younger, had a history of less exposure, and were less intellectually impaired than those who failed to obtain new jobs.

Edling et al[23] reported a follow-up study of two groups: 65 workers with symptoms but no impairment of psychometric test performance impairment, and 46 workers with mild chronic toxic encephalopathy (ie, symptoms and test performance abnormalities). Those with symptoms alone (type 1 solvent toxicity, according to the 1985 US solvent workshop classification[2] experienced improvement in certain symptoms (depression, concentration difficulties, and lack of initiative), when the results of the group are taken as a whole. Three of the 65 showed persistence of symptoms and deterioration of test performance leading to their being diagnosed as having mild chronic toxic encephalopathy on the second examination. Those 46 workers with mild chronic toxic encephalopathy on the initial examination generally showed persistence of symptoms and test performance decrements on follow-up testing. However, 12 of the 46 showed sufficient test performance improvement to be reclassified as type 1 solvent toxicity.

Morrow et al[24] reported some improvement in neuropsychologic test performance in persons with mild toxic encephalopathy following solvent exposure. Predictors of improvement in this group included lack of history of a "peak" exposure to solvents and absence of significant psychological distress.

In summary, these follow-up studies present a reasonably consistent picture. Persons showing symptoms only after solvent exposure show improvement after removal from solvent exposure or after significant exposure reduction. Persistent deficits in neurobehavioral function are observed in persons with more severe initial impairment even if additional exposure is totally eliminated. Some of those with persistent impairment suffer substantial limitations in functional ability and are persistently disabled.

Other Central Nervous System Effects. At least five case-referent studies of selected neurologic conditions have been performed in recent years to evaluate the association of solvent exposure with these disorders (Table 4). Another paper reported the results of a meta-analysis of 11 studies of Alzheimer's disease in which solvent exposure was evaluated.

Two studies examined groups receiving disability compensation for neuropsychiatric disorders. van Vliet et al[11] observed increasing likelihood of receiving disability compensation among Dutch construction workers as exposure increased; an exposure index was constructed using job history information. Brackbill et al[25] examined US Social Security records for persons receiving disability compensation for presenile dementia, alcoholism, affective psychoses, neurosis, personality disorders, and other diseases of the brain (International Classification of Diseases Code 347). They found an odds ratio for the painting occupation of 1.42 (95% confidence interval [CI]: 1.04, 1.94). These two studies are similar in design and results to that of Axelson et al,[26] one of the first studies to suggest a relationship between solvent exposure and neuropsychiatric disorders.

Four recent studies investigated more discrete neurologic disorders. O'Flynn et al[27] examined death certificates of 557 men who died from presenile dementia and found no evidence of increased rates of employment in solvent-exposed jobs in comparison with a matched control group (relative risk [RR], 1.14). Littorin et al[28] compared occupational histories of 104 cases of idiopathic focal epilepsy with matched referents and found that risk of disease increased with exposure level. Eighty-three multiple sclerosis patients were compared with referents by Flodin et al[29] and observed to have higher rates of solvent exposure (RR, 2.34). Hawkes et al[30] investigated patterns of employment in the leather industry of patients with motoneuron disease; the results are difficult to interpret for methodologic reasons.

The case-referent studies are quite varied in approach and results; in most instances, further research is needed to determine the significance of these findings. However, there appears to be some consistency of results between the three studies of persons receiving disability compensation. Together with the cross-sectional studies discussed above, these studies of disability pensioners raise concern that the disorders noted in cross-sectional studies of currently employed workers may lead to significant disability. This concern is best addressed scientifically through follow-up studies in which serial evaluations are performed on persons believed to have solvent-related encephalopathy.

One hundred eighty-seven paint manufacturing workers were tested by Schwartz et al[31] using the University of Pennsylvania Smell Identification Test. Nonsmoking solvent-exposed workers were found to have decre-

TABLE 4
Case-Referent Studies of Neuropsychiatric Disorders

Study	Cases	Exposure Measure	Odds Ratio
van Vliet et al (1989)[11]	Various neuropsychiatric disorders	Job history questionnaire	*
Brackbill et al (1990)[25]	Various neuropsychiatric disorders	Job history	1.47
O'Flynn et al (1987)[27]	Presenile dementia	Job title	1.14 (NS)
Littorin et al (1988)[28]	Focal epilepsy	Job title	*
Flodin et al (1988)[29]	Multiple sclerosis	Job history	2.3

* Increased disease risk with increased exposure.

ments in olfactory function correlated with increasing levels of exposure as measured by industrial hygiene sampling. The authors reviewed prior human studies, included case reports, that reported similar findings, along with animal studies showing effects of chemical exposure on the olfactory neuroepithelium. A smaller study by Sandmark et al[32] of 54 painters is difficult to interpret for methodologic reasons; the report is internally inconsistent and fails to present study results adequately.

Mergler and Blain[33] used two tests of color vision to evaluate 23 paint factory workers. Eighty percent of 10 highly exposed workers and 30.8% of 13 moderately exposed workers showed test abnormalities. The authors concluded that one of the tests, the Lanthony D-15 desaturated panel, is useful in screening exposed workers.

Ledin et al[34] used tests that evaluate posture control in 18 styrene-exposed workers and 9 patients with solvent-induced "psycho-organic syndrome." Posture control is regulated by input from the vestibular, visual, and proprioceptive systems into the cerebellum. Exposed workers were found to have increased amounts of postural sway on comparison with control subjects; patients with solvent encephalopathy showed even greater decrements in performance. No differences were noted in either group between test performance with eyes open or closed. The authors interpret these findings as providing evidence of cerebellar dysfunction attributable to solvent exposure. No consideration was given to possible confounding factors.

Ledin et al[35] performed follow-up studies of seven patients with chronic toxic encephalopathy using dynamic posturography. Testing in 1986 (reported by Moller et al[36]) showed abnormalities of posture consisting of increased body sway and impaired ability to cancel the vestibula-ocular reflex. Three years later, using somewhat different methods, the investigators observed persistent dysfunction in tests of posture control mechanisms.

Dager et al[37] report three cases of panic disorder precipitated by solvent exposure. Each person experienced the initial "panic attack" after workplace solvent exposure. Subsequent attacks occurred both at work and in nonwork situations usually after exposure to an olfactory stimulus. The authors describe the use of lactate infusion as part of the diagnostic process.

Prior to 1985, several studies reported electroencephalogram (EEG) abnormalities in workers exposed to styrene and in patients with "chronic solvent poisoning." Orbaek et al[38] performed a study of 32 workers with chronic toxic encephalopathy employing EEG power spectrum analysis; 24 of the 32 were retested 17 to 75 months later. Initial testing showed a doubling of the EEG power in all four recording channels; follow-up testing showed reduction in power but not to the level of the control group. The authors interpret the study as showing evidence of diffuse organic brain involvement.

Electrophysiologic tests measuring the cortical response to auditory, visual, and somatosensory have been used widely to diagnose certain neurologic disorders (eg, multiple sclerosis) and with increasing frequency in workers exposed to toxic substances. These techniques have been recommended by some as a way to evaluate central nervous system function because results are not influenced by the effort of the person tested.

Hazemann et al[39] studied 13 persons diagnosed as having psycho-organic syndrome using peripheral and somatosensory conduction studies. Peripheral conduction velocities and amplitudes were normal. In contrast, central conduction velocity was slowed; the degree of slowing of conduction was greater than that seen in a group of alcoholic persons tested using similar methods. Three subjects who were both solvent-exposed and alcoholic showed greater conduction slowing than any other group. Massioui et al[40] published a report on the same population showing normal auditory and visual evoked responses, in addition to the results noted in the Hazemann paper.

Moen et al[41] observed abnormalities in the cerebrospinal fluid (CSF) of 19 patients with chronic toxic encephalopathy (CTE). Elevated levels of protein, albumin, and IgG were observed; lowered concentrations of certain amino acids were also found. Taurine levels were negatively correlated with a solvent exposure index.

Barregard et al[42] performed a similar study of 23 patients with CTE and found a slight increase in CSF protein and IgG levels. The difference between patients and a matched control group was not statistically significant. Prior Swedish and Finnish studies discussed by the authors had failed to show CSF changes in similar populations.

Computed tomography scans of 62 CTE patients showed no evidence of structural brain changes when compared with control subjects in a study by Orbaek et al.[43] This study failed to confirm one prior "positive" study and was consistent with two other "negative" reports.

Diminished cerebral blood flow (7% lower than unexposed referents) was noted by Hagstadius et al,[44] when examining 28 patients with CTE. Repeated testing 24 to 84 months later showed persistent but less marked reductions in flow. The authors found these results consistent with prior studies of cerebral blood flow in solvent-exposed workers and a group of house painters.

In summary, these varied studies of other central nervous system effects show variable relationships with solvent exposure. Solvent-exposed workers may show evidence of loss of smell, as noted by Schwartz et al;[45] this study is methodologically sound and the findings are consistent with prior research. The observation of color vision loss in solvent-exposed workers, although of interest, requires further study to evaluate the results found by Mergler and Blain.[46] Several studies point to a mild effect of solvent-exposure on neurologic systems (predominantly the cerebellum) that control balance and posture. One follow-up investigation revealed persistent dysfunction 3 years after removal from exposure. The biologic signifi-

cance of these mild changes in test performance is unclear.

CSF concentrations of albumin and IgG may be elevated in solvent-induced chronic toxic encephalopathy patients. Such patients may also exhibit diffusely reduced cerebral blood flow. Structural changes, as measured by computed tomography, do not appear to be present in solvent-induced chronic toxic encephalopathy.

Electrophysiologic studies. Recent peripheral nervous system conduction studies revealed inconsistent findings: one was "positive," the other "negative." Earlier published research of this type has tended to show conduction abnormalities consistent with mild peripheral nervous system dysfunction. None of these studies has shown severe neuropathy of the type seen after exposure to *n*-hexane and other structurally similar hexacarbon solvents. EEG studies in solvent-exposed workers have tended to show diffuse changes consistent with diffuse cortical dysfunction.

1990 Conference on Organic Solvents and the Nervous System. In May 1990, the Commission of the European Communities and the Danish Ministry of the Environment convened an international conference on organic solvents and the nervous system. The conference was designed to review and discuss recent knowledge accumulated since a prior conference on the same subject held in Copenhagen in 1985.[1] The conference report provides essentially a summary of the presentations given and the opinions expressed by the participants. Although the conference was not designed to obtain consensus on particular issues, some summary views are expressed in the report.

Review of epidemiologic studies showed that solvent-exposed workers had (1) an increased risk of disability pensions for neuropsychiatric disorders; (2) excess neuropsychiatric symptoms, if currently employed; and (3) in most studies, lower performance in neurobehavioral tests, if currently exposed.

The clinical manifestations were believed to range from an affective syndrome, characterized by mood disturbances alone, to a severe chronic toxic encephalopathy, characterized by short-term memory impairment, fatigue, attention deficits, and other forms of cognitive change. This encephalopathy may be irreversible, but usually not progressive, upon cessation of exposure.

In summary, there was general agreement that the syndrome of chronic toxic encephalopathy, a term preferred over "dementia," does occur in workers with excess exposure to solvents. The condition may be associated with significant deficits in neurobehavioral function and, in some, may be sufficiently severe to result in permanent disability. The disorder does not seem to be progressive after cessation of exposure. Exposed persons identified at an early stage of dysfunction (ie, symptoms in the absence of neurobehavioral dysfunction) appear to recover total function without sequelae.

In addition to reviewing human research, the conference report discussed recent animal studies. These studies are less numerous and provide an incomplete view of the effects of solvents on exposed animals. Effects have been observed on brain morphology, brain biochemistry, and behavior. The relevance of these changes to the effects seen in humans is unclear.

Peripheral Nervous System

Certain solvents are recognized to cause a symmetrical distal sensorimotor peripheral neuropathy. Outbreaks caused by exposure to solvents such as *n*-hexane and methyl *n*-butyl ketone have been well documented[47] and the basic pathophysiology well delineated. Exposure to these solvents is limited to a relatively small segment of the work force. Many more are exposed to other solvents either singly or in mixtures; peripheral nervous system function in such groups has received limited attention.

Peripheral nervous system testing, by Orbaek et al,[38] of 32 chronic toxic encephalopathy patients (the same group described above) showed slowing of motor conduction in the median nerve that was more pronounced in follow-up testing 22 to 72 months later. Slowing in peroneal conduction velocity was observed only at the follow-up examination. Sensory conduction studies showed substantially reduced amplitude in median and sural nerves with a prolongation of the action potential in comparison with a control group; sensory conduction velocity in the median nerve was also slowed in the follow-up examination. Psychophysical tests measuring temperature sensation showed differences between the patient group and control subjects consistent with sensory decrement. The decrement in sensory function persisted in follow-up testing. The authors interpret these findings as indicating that exposure to solvent mixtures can cause a mild sensory neuropathy that is partially reversible after cessation of exposure.

Maizlish et al,[12] in a study of printers and spray painters, observed reduced two-point discrimination ability in the lower extremities but did not find reduced vibration sensation. The methods used in this study were the routine physical examination, a technique much less reproducible than the techniques used by others in three later studies. As part of a study using nerve conduction testing, Orbaek et al[38] observed slight changes in temperature sensitivity among 32 men with solvent-induced chronic toxic encephalopathy. These changes were observed in both the upper and lower extremities and remained unchanged when a portion of the group was retested 22 to 72 months after initial testing. Demers et al[48] observed similar deficits in vibration sensitivity among a group of commercial painters. Reduced vibration perception in all four extremities was noted in comparison with an unexposed control group.

Bove et al[49] used standardized tests of vibration and temperature perception to evaluate peripheral nervous system function in solvent-exposed construction painters. Threshold for perception of vibration in the lower extremities was raised in proportion to two indices of exposure to solvents over the previous year. Temperature

sensitivity was also effected in a similar manner.

In the study of Bleecker et al[5] (summarized above in the section on neurobehavioral studies), vibration sensation in the upper and lower extremities was evaluated using a standardized approach similar to that of Bove et al.[49] Elevated thresholds for vibration sensation were noted in the lower extremities; the degree of change was correlated with a lifetime exposure index.

In summary, workers exposed to solvent mixtures containing substances other than *n*-hexane and methyl *n*-butyl ketone have shown evidence of subclinical changes in sensory thresholds. These workers did not show evidence of clinical signs or symptoms. As discussed below, studies using nerve conduction testing have shown mild changes consistent with disruption of sensory nerve function (see Orbaek et al,[38] for example). Taken as a whole, these recent studies suggest that mild subclinical disruption in peripheral nervous system function does occur in workers exposed to solvent mixtures.

Neuropsychiatric Disorders

In contrast to the many studies of cognitive changes in solvent-exposed workers, few investigators have focused on personality changes. Morrow et al[50] observed a pattern of personality disturbances in 22 clinic patients with a history of solvent exposure. Using the Minnesota Multiphasic Personality Inventory, they observed increased rates of anxiety, depression, complaints of difficulty concentrating, and feelings of unreality and disturbances in thinking. The authors note striking similarities between these observations and those seen in posttraumatic stress disorder experienced by combat veterans.

Ryan et al[51] report an unusual syndrome, cacosmia, in a group of solvent-exposed workers seen in an occupational medicine clinic. Cacosmia is an olfactory hypersensitivity in which affected persons respond to neutral or mildly unpleasant odors (eg, hairspray, gasoline, or perfumes) with headaches, dizziness, and feelings of nausea. Decrements on neurobehavioral testing were observed in these workers.

McCrank and Rabhen[52] report four cases of progressive supranuclear palsy associated with solvent use. This condition is characterized by paralysis of external ocular movements, dysarthria, dysphasia, dystonic rigidity of the trunk and neck, and pseudodementia. The exposure histories of these four cases were varied and difficulty to evaluate.

Sleep apnea, initially associated with solvent exposure in a 1983 case report, was found in 7 of 15 patients with CTE.[53] Another group of 8 workers exposed to trichloroethane had a higher number of sleep apnea events (mean = 25/hour) than did a control group (mean = 2/hour).

These and other reports of various neuropsychiatric syndromes associated with solvent exposure are difficult to evaluate. Because solvent exposure is common, chance associations with these conditions of unknown etiology undoubtedly occur; these reports, even when presented as a series of cases, could represent chance associations. Heightened interest and attentiveness by the investigators to the possible association could have led to certain biases. Alternatively, as in the case of the original description of solvent encephalopathy by a Swedish occupational physician, these case series could represent genuine steps in our understanding of the varied manifestations of solvent neurotoxicity. Further study may resolve the dilemma.

Other Systems

Reproductive Effects

Spontaneous Abortion. In two separate studies of pregnancy outcomes in solvent-exposed women, increased rates of spontaneous abortion were noted. Lindbohm et al[54] used three Finnish data bases to identify 120 women who experienced spontaneous abortion and 336 control subjects with normal pregnancy outcomes. The odds ratio (OR) for solvent exposure was 2.2 (95% CI, 1.2 to 4.1) overall; women exposed to aliphatic hydrocarbons had a higher odds ratio for exposure (OR, 3.9; 95% CI, 1.1 to 14.2), as did women employed as graphics workers (OR, 5.2; 95% CI, 1.0 to 84.7).

Lipscomb et al[55] found a similar association in studying women employed in the electronics industry in California. First-trimester solvent exposure was associated with spontaneous abortion (OR, 3.34; 95% CI, 1.42 to 7.81). Those with regular or daily exposure showed a higher exposure risk (OR, 4.44; 95% CI, 1.86 to 10.58).

Congenital Malformations. McDonald et al[56] observed increased rates of urinary tract defect in offspring of women exposed to solvents. Toluene was the most common specific substance to which affected women were exposed. In the same study, the investigators failed to find an association between adverse reproductive outcomes and employment in various job categories without solvent exposure.

Tikkanen and Heinonen[57] observed slightly increased rates of cardiovascular anomalies, particularly ventricular septal defect, in women exposed to solvents during the first trimester of pregnancy. The relative risk of 1.3 was not statistically significant for all cardiovascular defects and marginally significant (RR, 1.5) for ventricular septal defect.

Other Effects on Offspring after Maternal Exposure. Eskenazi et al[58] performed detailed neurobehavioral evaluations on the children of solvent-exposed mothers at 3 to 4 years of age. No differences in neurodevelopment were noted when performance was compared with a matched control group.

Maternal Effects. Increased rates of preeclampsia in solvent-exposed women were noted by Eskenazi et al,[59] along with increased rates of pregnancy-associated hypertension. Relative risks, adjusted for confounding factors, were 3.9 and 3.0, respectively. The authors related this observation to reports of solvent-associated renal disorders (discussed below).

Effects of Paternal Exposure. Two investigations of paternal solvent exposure and reproductive outcome have appeared recently. Daniell and Vaughan[60] reported low birth weight in the offspring of male body-shop workers (RR, 1.6) and painters (RR, 1.4). The excess risk was noted only in full-term infants. Brender and Suarez[61] observed increased odds of paternal solvent exposure in cases of anencephaly (OR, 2.53). Painters showed the highest odds ratio at 3.43.

Genotoxicity. Kelsey et al[62] observed that acute exposure to solvents in construction painters was associated with increased rates of sister chromatid exchange (SCE), a measure of genotoxicity. The combination of a history of solvent exposure and of cigarette smoking was associated with an additive increase in SCE rate. Salamanco-Gomez et al[63] found similar changes in 35 children who were chronic abusers of solvents by inhalation. A ninefold increase in the rate of chromosome breaks was observed. Rates of SCE in exposed children were approximately 3 times that seen in unexposed comparison children.

Summary. In reviewing selected recent articles regarding reproductive effects of solvent exposure, an association appears to exist between maternal solvent exposure and increased risk of spontaneous abortion. Both studies summarized above noted moderate levels of risk (OR, 2 to 3); one study demonstrated increased risk with increased exposure levels. Effects on offspring after either maternal or paternal exposure are more difficult to interpret because each study summarized above deals with a different outcome and because little prior research exists to support the specific observations. Further study is needed. The observation that solvent-exposed mothers experience increased rates of preeclampsia is rather intriguing, particularly in view of other evidence of solvent-associated renal disease. This finding deserves particular attention in subsequent research. In view of its biological significance, further studies of genotoxicity in solvent-exposed workers should be given priority.

Cancer

Most recent studies and one review article that deal with the association between occupational solvent exposure and cancer development focus on malignancies of the lymphatic and hematopoietic tissues. Olsson and Brandt[64] observed an odds ratio of 3.3 for solvent exposure in a group of non-Hodgkins lymphoma patients. Cases that were localized to supradiaphragmatic sites showed a higher association with solvent exposure (OR, 6.5). Increasing duration of solvent exposure was associated with increased risk of lymphoma.

In a study of a cohort of dry-cleaning workers, Blair et al[65] observed increased standardized mortality rates for esophageal and cervical cancer that were statistically significant. Increased rates were also observed for other cancers including lymphosarcoma, reticulosarcoma, and Hodgkin's disease that were not statistically significant. Although the numbers of deaths were small, the greatest risk for cancers of the lymphatic and hematopoietic systems (standardized mortality ratio, 4.0) was seen in workers with heaviest solvent exposure.

Brandt et al[66] reviewed a variety of studies and observed that both Hodgkin's disease and non-Hodgkin's lymphoma have been associated frequently with solvent exposure; the level of association was moderate (OR, 3 to 7). Brandt also reviewed numerous studies that reported the well-established association between acute leukemia and benzene exposure, along with the limited studies relating myeloma and solvent exposure.

Hernberg et al[67] observed increased rates of liver cancer in Finnish women exposed to solvents. In a well-designed case-referent study, the investigators noted an odds ratio for exposure of 7.8. Men included in the same study did not show this association.

Brandt and colleagues[68] studied lymphoma cells from non-Hodgkin's lymphoma patients with solvent exposure and found consistent chromosomal aberrations. The specific changes, involving a translocation on chromosome 14, were not seen in patients without solvent exposure.

Renal Disease

Increased urine concentrations of erythrocytes, leukocytes, and albumin were noted by Hashimoto et al[69] in a group of 215 solvent-exposed workers. These findings are largely consistent with the observations of Hotz et al,[70] who found increased urine concentrations of erythrocytes, albumin, and *N*-acetylglucosaminidase in 148 solvent-exposed workers. Other studies published before 1985 have reported similar findings. In the Hashimoto study, these changes in urine were not associated with reduction in glomerular filtration rate, as noted by serum blood urea nitrogen and creatinine concentrations. Hashimoto et al[69] suggest that the cellular changes may derive from effects on the lower urinary tract.

One recent study by Harrington et al[71] investigated the association of solvent exposure with the occurrence of glomerulonephritis and renal cancer. Solvent exposure occurred no more frequently in 50 biopsy-proven cases of glomerulonephritis than in referent cases. No association with solvent exposure was noted for renal cancer. The authors compare these results with two other "positive" and one other "negative" study of solvent exposure and glomerulonephritis. No conclusions on the overall issue are drawn by the authors.

Following the summary of a case of glomerulonephritis in a 29-year-old man employed as an automobile cleaner (exposed to Stoddard solvent), Daniell and colleagues[72] reviewed the relevant literature. They found that despite acknowledged methodologic limitations, seven of the nine case-control studies published before 1988 showed statistically significant associations between solvent exposure and glomerulonephritis. The risk varied between 2.8 and 8.9; three studies found that the prevalence of glomerulonephritis increased with the intensity and direction of solvent exposure. Daniell et al[72] also reviewed other studies showing various abnormalities in renal function among solvent-

exposed populations. Navarte et al[73] presented one case report of chronic tubulointerstitial nephritis in a solvent-exposed worker; the patient also had a history of ulcerative colitis. Based on their review of prior animal and human research, the authors conclude that the case was probably caused by solvent exposure. Sesso et al[74] performed a case-control study of 17 patients with biopsy-proven crescent-c glomerulonephritis and 34 matched hospital control subjects. The relative risk for solvent exposure was 5.0 (95% CI, 1.14 to 22.00).

Summary. The literature regarding solvent-induced renal disorders has continued to grow in recent years. Consistent results have been obtained in several studies regarding changes in urine sediment and protein concentrations; solvent exposure appears to cause increased levels of erythrocytes and leukocytes in urine. The exposure level necessary to cause this effect is uncertain, as is the long-term significance of these findings.

The association between glomerulonephritis and solvent exposure continues to be difficult to assess despite several recent methodologically sound studies. On balance, the majority of the investigations show an association (three- to fourfold risk) between glomerulonephritis and solvent exposure. In some cases, an exposure-response relationship was seen. When it occurs, glomerulonephritis associated with solvent exposure tends to be of a particular type—rapidly progressive glomerulonephritis. A plausible biologic mechanism has been postulated: antiglomerular basement membrane antibody related to release of antigen after solvent exposure. Other types of renal disorders, such as disease of the renal tubules, may be associated with excessive solvent exposure. Further research is needed to explore those associations.

Liver

Although liver disease after exposure to certain solvents such as carbon tetrachloride is well recognized in the medical literature, relatively few recent reports of solvent-induced liver disease have appeared. With the exception of one outbreak due to dimethylformamide and one large cross-sectional study, recent papers have focused on case reports after heavy exposure and studies using more "sensitive" indications of hepatic function.

Redlich et al[75] reported on the results of an investigation of 58 workers exposed to dimethylformamide at a fabric coating factory. The study followed the occurrence of a case of acute toxic hepatitis in a 40-year-old man employed at the plant. Exposure to dimethylformamide occurred through inhalation and skin contact in the index case and other employees; appropriate ventilation and skin protection had not been used. Biochemical tests of liver function showed that 36 of the 58 (62%) workers had elevated blood concentrations of aspartate amino transferase or alanine amino transferase, indicating hepatic dysfunction. Improved work practices and removal of workers most severely affected resulted in improvement in most; some workers showed persistent elevations of liver enzyme levels.

Harrison et al[76] reported two cases of fulminant hepatic failure in workers exposed to nitropropane, a known hepatotoxin; one worker died. Hodgson et al[77] reported on a series of four patients with fatty liver disease and 1,1,1-trichloroethane exposure. This solvent has been used widely, in part because it has been believed to have little potential for hepatotoxicity; the authors of the case series feel that 1,1,1-trichloroethane may have a greater potential for causing liver dysfunction than previously recognized. Cordes et al[78] reported on two cases of toxic hepatitis after heavy exposure to methylene chloride and to solvent mixtures. Chen et al[79] reported on an extensive study of two paint manufacturing facilities and 22 spray-painting facilities involving a total of 180 workers. Increased levels of γ-glutamyltransferase activity was observed to correlate with severity of solvent exposure, after controlling for levels of alcohol consumption and other factors.

More sensitive measures of liver function—assessment of antipyrine metabolism and measurement of serum bile acid concentration—have been used in three studies. Dossing[80] found significant changes in antipyrine metabolism among jet-fuel–exposed workers. Bile acid concentrations were elevated in solvent-exposed workers studied by Franco et al.[81] Their results were similar to an earlier study of styrene-exposed workers by Edling et al.[82]

In summary, exposure at high levels to recognized hepatoxic solvents continues to result in cases of acute hepatitis, which in some cases may result in fatal fulminant hepatic failure. Most well-designed epidemiologic studies of workers exposed to other, more commonly used solvents have found little evidence of hepatic dysfunction under adequately controlled conditions.

Pulmonary

Since 1985, two reports of solvents in relationship to pulmonary dysfunction, specifically disorders of the airways, have been published. Harving et al[83] noted that asthmatics demonstrate a decline in forced expiratory volume in 1 second and symptoms of discomfort after inhalation challenge with a mixture of organic solvents. Lerman and Kipen[84] reported a case of reactive airways dysfunction syndrome in a worker after acute exposure to a mixture of solvents; after the acute exposure episode, she continued to experience chest tightness when exposed to a variety of irritant substances. In summary, airways disorders (exacerbation of asthma or development of reactive airways dysfunction syndrome) have been associated with solvent exposure.

Cardiovascular

Cardiovascular disorders in relationship to solvent exposure were recently reviewed by Wilcosky and Simonson.[85] The role of carbon disulfide in the etiology of cardiovascular disease is well recognized. Methylene chloride is metabolized to carbon monoxide, leading to elevated blood concentrations of carboxyhemoglobin; significant acute exposures can aggravate existing coronary artery dis-

ease, in some cases possibly leading to fatal myocardial infarction. Mortality studies of methylene chloride-exposed workers have provided some evidence of increased cardiovascular disease rates. Other solvents have been associated with cardiac arrhythmias (eg, 1,1,1-trichloroethane and fluorocarbons). Fatal myocardial degeneration was reported in a man who chronically abused solvents for more than 5 years.[86] In summary, certain solvents have been associated with specific cardiovascular disorders: carbon disulfide and methylene chloride with coronary artery disease; 1,1,1-trichloroethane and certain fluorocarbons with cardiac arrhythmias.

Skin

Dermatitis is well recognized as an effect of chronic cutaneous exposure to various solvents. Yakes et al[87] reported increased rates of dermatitis in solvent-exposed newspaper pressroom workers. Eighteen of 212 (8.5%) exposed workers had evidence of eczematous dermatitis on examination.

Hematopoietic System

Increased red blood cell volume and decreased red blood cell counts in car repair painters and mechanics were reported by Beving et al.[88] The significance of these findings is unclear.

Related Issues

Solvent Abuse

Although the exposures are dramatically higher in solvent abusers than in occupationally exposed persons, some relevant information can be obtained from studies of solvent abuse. Morton[89] recently reviewed the literature on solvent abuse in children and adolescents. From that review and other literature, several points deserve attention. First, solvents have an inherent potential for acute intoxication and abuse. In the workplace, this potential may result in workers acting in such a way that exposure is increased so that the intoxicating effects, which some experience as a positive sensation, can be experienced. Second, chronic abuse has resulted in encephalopathy associated with cerebral atrophy, cerebellar degeneration, and peripheral neuropathy. As noted above, these syndromes are associated with excessive occupational exposure. Finally, those who abuse solvents, particularly as adolescents, have been noted to abuse alcohol and other drugs, either simultaneously or in later life.

Ethanol Consumption

Certain solvent-exposed occupational groups (eg, construction painters) may consume alcohol to a greater extent than other occupational groups (eg, other construction workers) that are similar socioeconomically. Fidler et al[90] observed significantly greater occasions of moderate and heavy drinking in construction painters than in drywall tapers who belonged to the same labor union, had similar levels of education, and who were of similar socioeconomic status. The reasons for this increased level of consumption are unclear. Some speculate that selection factors may operate: those who are moderate or heavy drinkers may choose an occupation (eg, painting) in which such behavior is common. Others relate drinking patterns to the circumstances (ie, social isolation) or the exposures (eg, solvent fumes) of the job by hypothesizing that these job factors may contribute to ethanol consumption.

There are interesting similarities between the health effects of various industrial solvents and ethanol. Ethanol is in fact used as a solvent in certain industrial processes. Both industrial solvents and ethanol cause acute and chronic central nervous system disorders that have similar features. The syndromes of acute solvent and ethanol intoxication are both described as "being high." Chronic toxic encephalopathy due to solvents is characterized by neurobehavioral deficits similar to those seen after chronic ethanol intake (eg, psychomotor and short-term memory deficits). Abuse of both solvents and ethanol is well recognized. In addition to neurotoxicity, both may cause liver dysfunction.

Exposure to solvents may potentiate the acute effect of ethanol consumption, possibly through competition for certain metabolic pathways. Chronic consumption of ethanol may potentiate the toxic effects of solvents (eg, somatosensory evoked potentials[91]).

Our understanding of the health effects of solvent exposure may be improved by comparative examination of the much more extensive literature on the chronic effects of ethanol consumption. Furthermore, prevention of solvent-induced disorders may benefit from examination of strategies that relate to ethanol consumption.

Prevention Strategies

As in all occupational disorders, the most basic strategy for prevention of exposure-induced disorders is to control exposure. In the case of solvent toxicity, substitution of non-solvent–containing products for those containing solvents has occurred. Particularly, substitution of water-based paints for solvent-based paints has occurred with attendant health benefits. However, in using water-based paints, the exposure hazards should also be carefully considered. If substitution of a less toxic product does not occur, exposure control through appropriate industrial hygiene measures should be accomplished.

In selecting people to work in a solvent-exposed position, medical evaluations should be performed to identify those who have conditions that could be aggravated by solvent exposure (eg, asthma, peripheral neuropathy, skin disorders). This approach could be carried further in an attempt to identify persons with cognitive deficits on neurobehavioral testing; however, this has not occurred. If it were attempted, significant legal and ethical concerns would undoubtedly arise.

Although no reports exist of excluding persons with a history of alcoholism or current heavy alcohol consumption from solvent exposure, a medical justification may exist for such action. Because heavy alcohol consumption may potentiate both the acute and chronic neurotoxic effects of solvents, persons with such a his-

tory could be assumed to be at increased risk. Again, significant legal and ethical considerations would apply to policies that exclude persons with heavy alcohol consumption from solvent-exposed jobs.

Periodic biologic monitoring of solvent-exposed workers has a theoretic basis but has not occurred widely. Because some solvents are metabolized to substances that can be measured in blood, urine, or exhaled breath, biologic monitoring can be performed. The half-life of these metabolites is short and therefore sample collection must be timed carefully to relate directly to exposure periods. As a result, biologic monitoring is often impractical under normal working conditions.

Use of neurobehavioral tests or other tests of organ system function (eg, peripheral nervous system or liver) for periodic testing of exposed workers has not occurred commonly in solvent-exposed populations. Both theoretic and practical considerations limit such use in most settings.

Summary

Prevention of solvent-induced disorders relies heavily on strategies designed to control exposure. The most important of these include substitution of less toxic products, use of ventilation systems, and use of personal protective equipment to reduce skin and respiratory absorption.

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Interesting Quotations

. . .the case was only one incident in one physician's experience. Although his memory of that experience remains vivid, it is best viewed as an anecdote from which it would be a mistake to generalize. The plural of "anecdote" is not "data."

From *Enemies of Patients*, by R. Macklin. New York: Oxford Press; 1993, p 8.