The effect on memory of long-term exposure to organic solvents: a critical review

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Abstract

This review compares memory test results derived from studies revolving around the effect on memory of long term exposure to organic solvents. The comparison presents a variety of conclusions offered by the different researchers. The spectrum of conclusions ranges from negation of any effect on memory of organic solvents, to confirmation of memory decline under such exposure. Analysis of the findings does not determine conclusively whether or not there is a decline in memory resulting from long-term exposure to organic solvents. The difficulty in drawing conclusions is due to disparate methodologies, populations which differed in age, educational level, type of occupation, and the variety of exposure agents. In addition, memory tests used in the various studies differ significantly. The significance of each factor is discussed.

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In recent years there has been an increase in awareness of potential deleterious effect on workers' central nervous system (CNS) due to long term exposure to various chemicals used in industry. Organic solvents are among the chemicals which have been studied extensively. The most common symptoms ascribed to CNS involvement are increased fatigue, memory impairment, concentration difficulties, and personality changes (Antti-Poika, 1982; Arlien-Soborg, 1979; Foldin, Elding, & Axelson, 1984; Elding, 1985; Hannien, Antti-Poika, Juntunen, & Koskenvuo, 1991). Early detection of these problems is rarely uncovered by physical examination, which is inefficient in detecting abnormalities. Memory is frequently reported as a very sensitive measure to CNS impairment (Arlien-Soborg, 1985; Baker & White, 1985; Gupta, Kumar, & Srivastava, 1990).

Suspicions were initially raised in the middle of 1950's by Grandjean (1955) and later, in the early 1970's, by clinical observations of a Swedish psychologist studying memory loss in two workers in the sports boats and swimming pool industry, who had undergone heavy exposure to styrene (Baker, Smith, & Landrigan, 1985). Since then, numerous systematic studies have been conducted (Anshelm-Olson, 1982; Bleeker, Bolla, Agnew, Schwartz, & Ford, 1991; Grasso, 1988; Gregersen, 1988; Hane et al., 1977; Hanninen, 1979, 1988; Hasman, 1980; Kilburn, Seidman, & Warshaw, 1985; Linstrom, 1981; Linz et al., 1986; Maximilian, Risberg, Prohovnik, Rehnstrom, & Haeger-Aronsen, 1982; Mark, Winkel, & Gyntelberg, 1988; Orbaek & Nise, 1989; Spurgeon et al., 1992). However, the findings of these studies are inconsistent: some support the notion that organic solvents affect memory; other studies report no such effect; while yet other studies report mixed results. Thus, the purpose of the present paper is twofold: first, to review studies that have tested the effects of organic solvents on memory, and, second, to trace and identify relevant variables, which were not appropriately controlled and that might have affected the results.

Neuropsychological testing is significant since it is sensitive enough to detect even minimal disturbances. Tests may be administered in many diagnostic and treatment settings and may help in screening large groups of hazard-exposed subjects (Baker & Smith, 1984). Most studies which try to detect cognitive problems include a variety of cognitive tests (in whole or in part) which evaluate the following abilities: psychomotor speed, manual dexterity, attention, mental flexibility, perception, visio-spatial ability, general intelligence, learning ability, memory, etc. (Grandjean, 1989; Hanninen, Eskelinen, Husman, & Nurminen, 1976; Hanninen & Luukkonen, 1985; Hogstedt, 1980; Ryan, Morrow, & Hodgson, 1987; Valciukas & Lilis, 1980)

Memory impairment is particularly evident, leading to difficulties in everyday activities and in ability to adapt to new situations which require learning new information. Despite the vulnerability of memory to CNS damage, very few studies focus on memory itself. Most studies include memory tests along with many other cognitive tests that utilize just a few brief memory test components. This bias hampers the ability of the study to provide an accurate evaluation, including an analysis of results and definitive conclusions regarding the different aspects of memory.

Thirteen studies are included in this review. We have excluded case reports.

Studies testing the effects of organic solvents on memory

As can be seen in Table 1, two of the studies reviewed reported no memory impairment following long term exposure to organic solvents.

As can be seen in Table 2, seven of the studies reviewed reported memory impairment following long term exposure to organic solvents.

Table 1
Studies in which no effect on memory was observed

	EXPOSED POPULATIONS						
Reference	Age (mean) (yrs.)	Education (mean) (# of yrs.)	Occupation	Duration of exposure (mean)(yrs.)	TYPE OF MEMORY	TEST	SOURCE
Triebig et al. (1988) (N=105)	..	..	house painters	27 (median)	Short-term	KAI-TR	Lehrlet
					Speed of information transfer to memory	KAI-CVW	..
					Quotient of memory	KAI-GO	
Gregersen et al. (1984) (N=65)	39.5	7.8	* painters * print & lacquer industry * dry cleaning * photo-gravure	12.9	Short-term: visual and verbal	Word pair -	Willanger (1970)
					Immediate and inter-mediate: visual	Picture recognition	Cronholm and Molander (1957)
					Immediate and inter-mediate: visual	Visual gestalt	Andersen (1976)
					Short-term: verbal	Story recall	Binet-Simon (1961) Wechsler (1945)
					Immediate: verbal	Sentence recall	Binet-Simon (1961)

- = no effect was observed .. = data not available

Table 2
Studies in which an effect on memory was observed

	EXPOSED POPULATIONS						
Reference	Age (mean) (yrs.)	Education (mean) (# of yrs.)	Occupation	Duration of exposure (mean)(yrs.)	TYPE OF MEMORY	TEST	SOURCE
Linz et al. (1986) (N=15)	15-56 (range)	7.8	industry painters	weeks to 20 years	Short-term: tactile	Tactual perf.	Halstead / Reiten
					Immediate and intermediate	Auditory verbal learning test	Rey (1964)
					Short-term: digits	Digit span	Wechsler (1945)
Orbaek et al. (1989) (N=30)	50	..	photo-gravure printers	20 (median)	..	Structural review	..
					Spatial	Visual retention test	Benton (1974)
Kilburn et al. (1987) (N=305)	40	..	histology technicians	17	Verbal	Story recall	..
					Short-term: visual	Visual reproduction	Wechsler (1945)
					Short-term: verbal	Logical memory	Wechsler (1945)
Hanninen et al. (1976) (N=100)	35	..	car painters	..	Short-term: digits	Digit span	Wechsler (1945)
					Short-term: verbal	Logical memory	Wechsler (1945)
					Short-term: verbal	Associate learning	Wechsler (1945)
					Visual	Visual retention test	Benton (1974)
Gregersen (1988) (N=59)	46.1 I 49.4 II	..	* painters * prints & lacquer industry * dry cleaning * photo-gravure * boat ind.	12.9 I 18.4 II	..	Structured interview	..
Kilburn et al. (1985) (N=76)	40.8	..	histology technicians	12.8	Short-term	Structured interview	..
					Long-term	Structured interview	..
Winchester et al. (N=42)	..	..	industry painters	..	..	Structured interview	..

+ = adverse effect was observed .. = data not available

Table 3
Studies in which a mixed effect on memory was observed

	EXPOSED POPULATIONS							
Reference	Age (mean) (yrs.)	Education (mean) (# of yrs.)	Occupation	Duration of exposure (mean)(yrs.)	TYPE OF MEMORY	TEST	SOURCE	RESULTS
Stollery et al. (1988) (N=24)	33.7	..	Adhesive in tennis ball industry	5.3	Immediate verbal	Paired assoc. task	..	
					Immediate verbal	Social position task	..	
					Delayed verbal	Brown-Patterson task	..	+
Ryan et al. (1988) (N=17)	41.5	..	blue-collar workers	12.2	..	Incidental memory	Ryan, Vega & Drash (1985)	+
					Verbal	Verbal learning	..	+
					Delayed verbal	Delayed verbal learning	..	+
					..	Symbol digit learning	Ryan & Butters (1980)	-
					Delayed	Delayed digit learning	..	+
					..	Receiving words	..	-
Moen et al. (1990) (N=75)	42	8 - simple workers 11 - qualified workers	seamen	22	Immediate: visual	Elizer test of psychoorganic	Elizer (1969)	-
					Short-term: verbal	Memory span task	Luria (1976)	+
Elofsson et al. (1980) (N=45)	25-65	..	car painters	..	Visual	Visual retention test	Benton (1974)	-
					Visual	Memory test recognition	Stockholm Univ.	-
					Visual	Memory test reproduction	Stockholm Univ.	+

+ = adverse effect was observed
- = no effect was observed
.. = data not available

Arlien-Soborg (1985) reported a study in which 90% of the house painters, who participated, suffered from memory impairment; there were fewer other significant cognitive problems encountered. Baker and White (1985) emphasize the vulnerability of memory in workers, who suffer from mild and severe chronic toxic encephalopathy. Individuals with mild chronic toxic encephalopathy typically show evidence of memory and psychomotor function impairment.

As can be seen in Table 3, four of the studies reviewed reported mixed effect on memory following long term exposure to organic solvents.

In contrast with the two researchers who report that decline in memory cannot be observed after long-term exposure to organic solvents (Gregersen et al., 1984; Triebig et al., 1988), seven others do find significant decline in memory as a result of long-term exposure to organic solvents (Gregersen, 1988; Hanninen et al., 1976; Kilburn et al., 1985, 1987; Linz et al., 1986; Orbaek & Nise, 1989; Winchester & Madyar, 1986). However, on closer examination it appears that three of the seven studies base their results on questionnaires, which are liable to be inaccurate instruments for detecting symptoms of mental impairment (Grandjean, 1989).

Two major characteristics may be observed in the different studies: a) evaluation of the spectrum of memory ranging from short-term to long-term; and b) visual versus verbal memory, with the addition of digit recall. The results of the memory tests which evaluate short, intermediate and long-term memory are as follows: nine test results indicate that an effect on short-term memory was observed (Hanninen et al., 1976; Kilburn et al., 1985, 1987; Linz et al., 1986; Moen, Riise, Haga, & Fossan, 1990), while seven demonstrate no such effect (Gregersen et al., 1984; Stollery & Flint, 1988; Moen et al., 1990; Triebig et al., 1988). Immediate and intermediate memory when evaluted as a single unit showed the following results: results of two tests show a decline in memory (Hanninen et al., 1976;

Linz et al., 1986), while three others observe no effects on memory (Gregersen et al., 1984; Elofsson et al., 1980). Of the four tests reporting on long-term memory, three report that an effect was observed (Kilburn et al., 1985; Ryan et al., 1988; Stollery & Flint, 1988), and only one test shows no effect on long-term memory (Ryan et al., 1988). Divergent test results concerning visual, verbal and digital memory are evenly distributed as well. Five visual tests found a decline in memory as a result of long-term exposure (Elofsson et al., 1980; Hanninen et al., 1976; Kilburn et al., 1987; Linz et al., 1986; Orbaek & Nise, 1989) but six other tests found no such decline (Elofsson et al., 1980; Gregersen et al., 1984; Moen et al., 1990)

We may conclude from the above that neither the number of studies nor their characteristics help us solve the dilemma concerning the influence of chronic exposure to organic solvents on memory decline.

Variables that may be relevant to effects of organic solvents on memory

The studies reviewed in this article present different and even contradictory results. This divergence may be inherent in each study's disparate methodological approach, since different tests with different testing methodologies were used to evaluate memory. Although all populations examined were exposed to organic solvents, populations differed considerably, especially regarding specific types of occupations with differing environmental conditions, including different exposure agents, investigated in all the surveys. Now we will focus on each of the above variables and judge its effect on the findings.

Exposed populations

The fact that populations in all the studies were exposed to organic solvents seems to be the only population-related variable in common. Other than that, populations differ in age,

education, occupation, exposure agent and duration of exposure to the agent. All these factors are discussed below.

Age and educational level

The common protocol (Grandjean, 1989) which aims at an international collaborative study on the chronic effects of organic solvents emphasizes that "the major potential confounder and interacting factors of neurobehavioral performance are age and primary intellectual ability" (p. 22). Indeed, Elofsson et al. (1980) reported that age affected memory, in addition to the number of years of exposure, since years of exposure were not correlated with age. Moen et al. (1990) mention the correlation between auditory and visual memory and age in both exposed and non-exposed subjects (no significant difference was found in visual memory between the groups). Kilburn et al. (1987) found a correlation between age and the Wechsler Memory Scale (Wechsler, 1945) only. Triebig et al. (1988) described trends toward correlation between memory test results and age. Ryan et al. (1988) found no correlation between memory and age. Despite its essential place in evaluating primary intellectual ability, educational level was controlled in only three of the studies mentioned (Gregersen et al., 1984; Moen et al., 1990; Ryan et al. 1988). There is no report on correlation between educational level and memory. Ryan et al. (1987) tried to confirm standards for different neuropsychological tests (among them, memory) for blue collar workers. They found that all test scores were affected significantly by age and education. Because of the strong relationship between age, education and performance, the authors "corrected" test scores for the effects of age and education by making use of regression coefficients derived from normative studies. This might have been useful, had it been applied to more than five memory tests, of which only one was a test used in common cognitive batteries. It may be assumed

that were such normative scores available, many of the discrepancies would have been reduced.

Duration of exposure

The duration of exposure to organic solvents differed from one study to the other, ranging from one to ten years. Ryan et al. (1988) required at least one year of exposure as the inclusion criterion for participation of subjects in his research. Triebig et al. (1988) and Orbaek and Nise (1989) were interested in workers exposed to organic solvents during a period of at least 10 years. At the same time, workers included in the research studies were divided into subgroups with differing exposure criteria. Ryan et al. (1988) subdivided his population according to the number of years of exposure to organic solvents. Triebig et al. (1988) made other adjustments to the exposure criteria, adding variables for the number of exposure hours per day and work place conditions. Elofsson et al. (1980) added a variable for the type of protection provided in the work place, while Gregersen et al. (1984) added occupational history as an adjustment variable. Such a broad definition of the term "duration of exposure" might affect the results of memory tests and make it difficult to draw a general conclusion regarding significance of duration of exposure for the results. Gregersen et al. (1988) found a significant correlation between the two variables, Triebig et al. (1988) found a correlation only between short-term memory and duration of exposure, and Moen et al. (1990) reported a correlation with auditory memory only. In contrast, Ryan et al. (1988) found no correlation between duration of exposure and memory but did report two significant variables: time elapsed between last exposure and the examination, and any past episodic (versus periodic) exposure incidents.

Occupation

The subjects in all studies reviewed here were employed in different occupations, thus creating different environmental

conditions even where the exposure agent is the same. Triebig et al. (1988) examined a population of house painters; Elofsson et al. (1980) examined a mixed population of house and industrial painters; Moen et al. (1990) used seamen as his target population; while Gregersen et al. (1984) evaluated, in the context of one survey, workers from different occupations - painters, workers in the print and lacquer industries, in dry cleaning and in photogravure. In addition, Linz et al. (1986) and Ryan et al. (1988) examined workers in various types of jobs, who were exposed to organic solvents and who voluntarily sought medical help following a decline in memory. It cannot be expected that the results of memory test for the latter population would be the same as those of random samples of exposed workers from different work places, who consider themselves perfectly healthy.

Exposure agent

Varying occupations provide different mixtures of organic solvents; this article reviews at least 20 different mixtures under the category of organic solvents. Only one study deals with exposure of photogravure printers to pure toluene (Orbaek & Nise, 1989). Hanninen (1979) compared psychological performance in various types of occupational intoxication. Comparison of memory tests showed significant decline in memory due to long-term exposure to mixtures of organic solvents on all memory tests (four visual and verbal memory tests). Workers exposed only to styrene did not suffer from memory impairment, while workers exposed only to toluene failed on two memory tests but succeeded on two others.

This review emphasizes the possible different effects on memory of exposure to different agents. A survey of the studies included does not allow for reworking of results relating to the specific type of solvent to which workers were exposed. It is quite possible that different organic solvent mixtures have

different effects on memory, as the results of the tests described above would seem to indicate.

Memory tests

In the 13 studies that included memory tests and that specify the tests' authors, only two tests were used by more than one researcher: the Wechsler Digit Span Subtest (1945) and the Benton Visual Retention Test (1978). The Digit Span Subtest of the WMS (Wechsler, 1945) was used by Hanninen et al. (1976), Linz et al. (1986), and Kilburn et al. (1987). The Benton Visual Retention Test was used by Hanninen et al. (1976) and Elofsson et al. (1980). Researchers such as Ryan et al. (1987, 1988) and Gregersen et al. (1984, 1988) who published more than one study, tended to reuse the same set of tests used in the first of their studies.

A comparison of the test results shows that all three studies found significant impairment on the Digit Span Subtest. This certainly testifies to the sensitivity of this test as a tool for evaluating long-term exposure to organic solvents. However, it is important to note that this subtest is considered as a measure of attention rather than a memory measure (Lezak, 1983). Aside from this finding, no conclusion can be drawn from the types of memory tests. Even the division into such categories as visual memory versus verbal memory, immediate versus delayed, etc. (without relating to the test itself), did not produce any uniformity in the results. Studies which evaluate subjective reports as a criterion for determining memory decline used a non-uniform structured questionnaire that reported subjective complaints regarding memory impairment (Gregersen et al., 1988; Kilburn et al., 1985; Winchester et al., 1986).

It is clear that the researchers' aim to discover specific effects on memory after long-term exposure to organic solvents, impaired their ability to arrive at an overall view of memory and to reach definitive conclusions. It seems that in order to

achieve a breakthrough in this field, the WHO (1989) recommendations for evaluating effects on the CNS must be followed. Agreement on some basic definitions and principles concerning study design and applied methods are essential.

The WHO/EURO Working Group (Copenhagen, 1985) which studied the chronic effects of organic solvents on the CNS recommended establishing a commonly accepted categorization of neuropsychological functions, an accepted linking of specific tests to those functions, and a standard vocabulary for discussing those functions and tests (Grandjean, 1985). It is unfortunate that no such common agreement is reflected in the studies reviewed in this article. Even the core protocol for international collaborative study (Grandjean, 1989) includes no recommendations for memory evaluation among these "obligatory tests and strongly recommended tests" (p. 17).

We recommend use of memory tests and batteries that provide a range of scores representing different aspects of learning and memory. Such tests would include the Wechsler Memory Scale - Revised (WMS-R) (Wechsler, 1987) which provides verbal and visual memory scores for immediate and delayed recall. The Rey - Auditory Verbal Learning Test (AVLT) (Rey, 1964) is also recommended, since it can provide measures of learning ability, sensitivity to proactive and retroactive interferences, delayed recall and recognition.

We hope that this review will heighten awareness and emphasize the importance of controlling all variables that might influence the effects on memory of long term exposure to organic solvents. We expect this will lead to more conclusive results in this area.

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