

Review Article

Impairment of Neurobehavioral Function and Color Vision Loss among Workers Exposed to Low Concentration of Styrene—A Review of Literatures

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Abstract: Recently many studies on the health effects of workers who exposed to low-concentration styrene have been published. In this paper firstly we mentioned the reasons why nervous system was critical organ for evaluating the toxicity of organic solvents both in the acute and chronic exposure phases. Then we indicated how neurobehavioral test batteries were useful to detect subclinical adverse health effects of workers exposed to organic solvents. Secondly we reviewed many epidemiological studies on the impairment of neurobehavioral function, i.e., perceptual speed, memory, cognition, personality and mood, and the loss of color vision among styrene workers. Finally, we showed our recent data on the relationship between color vision loss and the concentration of urine metabolites among styrene workers. It can conclude that styrene may cause damage on nervous system, even at the low exposure level such as 50 ppm which used to be the Threshold Limit Value (TLV) recommended by Japan Society for Occupational Health (until 1999) and American Conference of Industrial Hygienists (until 1997).

Key words: Neurobehavioral test batteries, Color vision loss, Styrene, Occupational exposure

Background

Organic solvents are used in a wide range of processes in the industrial work place, particularly in the plastics, graphics and metal industries, in the manufacture of paints, lacquers and adhesives and in dry cleaning. Because most organic solvents are volatile liquids at room temperature and are lipophilic¹⁾, they easily bind to lipid-rich tissues such as the brain, myelin and adipose tissue. Therefore, the neurobehavioral effects of organic solvents need to be carefully evaluated. Table 1 presents the reasons why neurobehavioral evaluation is important. First, neurotoxicity is one of the most sensitive indicators, i.e. in ACGIH, for

about 30% chemicals, the threshold limit values are established by concerning neurobehavioral effects as most sensitive adverse effects²⁾. Secondly, there is almost no effective clinical treatment for neurological disorders. Therefore, the functional recovery after the cessation of

Table 1. The importance of evaluating the neurobehavioral effects of organic solvent toxicity

- 1) Neurotoxicity is a more sensitive indicator of health effects than other toxicities.
- 2) There is no effective clinical treatment for neurological damage.
- 3) Neurotoxicity may cause behavioral abnormality and changes of human character.
- 4) Organic solvents are transferred to the fetus through the placenta and may affect neural development.

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Table 2. Representative test batteries for evaluating the neurobehavioral effects of organic solvents

Function tested	Evaluation	Method
Verbal	Similarities	choose similar words
Psychomotor	Reaction Time*	press a key as quickly as possible in response to a figure presented on a display
	Finger Tapping	tap a finger as quickly as possible
	Aiming Test*	dot as quickly as possible
	Santa Ana*	half rotate as many pegboards as possible
	Mira Test	copy a figure in a mirror
Perceptual motor speed	Digit Symbol*	write the digits corresponding to certain symbols as fast as possible
Short-term memory		
Visual memory	Benton Retention Test*	memory figure pattern
Verbal memory	Digit Span*	recite a sequence of numbers
	Associative Learning	memory connected two words
Cognition		
Visual spatial	Block Design	complete blocks
Personality and Mood	MMPI	evaluate one's personality from
	POMS*	evaluate one's mood (tension, anger, fatigue, depression, liveliness, confusion) from replies

*: WHO neurobehavioral core test battery (NCTB).

exposure is slow and sometimes there exist long-lasting residual effects. Thirdly, neurotoxicity sometimes cause behavioral changes in people exposed to organic solvents. Fourthly, some organic solvents are known to be able to transfer to the fetus through the placenta and adversely affect the neurobehavioral development of succeeding generations.

Unlike the other effects of human occupational exposure to organic solvents, risk evaluation for neurobehavioral effects is not easy. Several reasons for this difficulty exist; 1) subjective and objective symptoms of neurotoxicity are usually latent and are often missed, 2) the pattern of neurological damage for many solvents is not specific, 3) the tests used in clinical settings are often not quantitative and their sensitivities are low, 4) the causal relationship between observed damage and exposure to solvents is sometimes unclear, 5) the latent period makes the causal relationship more unclear, and 6) there is little data available on the morbidity rate of neural damage or illness among epidemiologically definite populations.

Since the early 1970s, neurobehavioral test batteries have been developed, beginning in Europe, for evaluating neurobehavioral dysfunction caused by exposure to organic solvents. Representative test batteries and the function evaluated by each test are shown in Table 2. In addition to the neurobehavioral function listed, some sensory nervous system functions (peripheral nerve velocity, color vision, hearing threshold, etc.) have also been evaluated. In Japan,

the detection of acute or chronic neurobehavioral effects and the establishment of occupational permissible values for organic solvents have been achieved by the use of these neurobehavioral test batteries³⁾.

In this paper, we review recent research on the neurobehavioral effects of human occupational exposure to styrene, an organic solvent used world-wide in industrial workplaces, and report the results of our study of the effects of exposure to styrene on color blindness.

Impairment of Neurobehavioral Function

Psychomotor function

In the existing literature on neurobehavioral testing in solvent-exposed populations, differences between the exposed and unexposed subjects were most commonly observed during tests of psychomotor function.

To assess coordination function, Lindstrom *et al.* performed the Mira test on 98 styrene-exposed male workers (mean exposed concentration: 25 ppm) and compared the results with those obtained from 43 control subjects⁴⁾. They reported that psychomotor function in the styrene-exposed group was statistically lower than that in the control group and that in a multiple regression analysis, poor psychomotor performance proved to correlate with a high urinary mandelic acid concentration. Flodin *et al.* also reported that the Cylinder test performance of the high styrene-exposed group

Table 3. A reviews of literatures on neurobehavioral effects of chronic occupational exposure to styrene

Author (year, country)	Number of subjects		Exposure level* (ppm)	Exposure period (years)	Tested function				
	Exposed	Control			Psychomotor	Perceptual motor speed	Memory	Cognition	Personality and mood
Lindstrom (1976, Finland)	98	43	25	4.9	+				
					(Mira Test)				
Cherry (1980, England)	26	26	92	n.s.	+	-			+
					(Reaction Time)	(Digit Symbol)			(Visual Analogue Scales)
Cherry (1981, England)	17	0	20	n.s.	+				
					(Reaction Time)				
Mutti (1984, Italy)	50	50	10-300 (range)	8.6				+	+
								(Block Design)	(Logical Memory)
Flodin (1989, Sweden)	17	0	5.9	11.6	+	-	-	-	
					(Cylinders)	(Digit Symbol)	(Benton)	(Block Design)	
Schoenhuber (1989, Italy)	55	0	25	n.s.	-	-			
					(Reaction Time)	(Digit Symbol)			
Letz (1990, U.S.A.)	105	0	29.9	2.9		+			
						(Digit Symbol)			
Fallas (1992, France)	60	60	24.3	6.5	-	-	-		
					(Reaction Time)	(Digit Symbol)	(Digit Span)		
					-		-		
					(Santa Ana)		(Benton)		
Yokoyama (1992, Japan)	11	11	26	4		-			-
						(Digit Symbol)			(MMPI)
Edling (1993, Sweden)	20	20	8.6	9	-	-			
					(Reaction Time)	(Digit Symbol)			
Jegaden (1993, France)	30	30	22.7	5	+		+		
					(Reaction Time)		(Digit Span)		
							+		
							(Choice Reaction Time)		

*: mean exposed concentrations are shown. n.s.: not shown, +: affected, -: non-affected.

(n=9, mean exposed concentration: 11.8 ppm) was significantly worse than that of the low-exposed group (n=8, exposed concentration: below 5.9 ppm)⁵. However, Fallas *et al.* (n=60, mean exposed concentration: 24.3 ppm) reported that there were no differences in Santa Ana test results between styrene-exposed workers and controls⁶.

Cherry *et al.* performed a simple reaction time test to evaluate the speed and coordination function of styrene-exposed workers⁷. The reaction times of 26 exposed workers (mean exposed concentration: 92 ppm) were significantly lower than those of 26 controls. They also examined the relation between styrene metabolism and reaction time. The rate of clearance of mandelic acid was found to differ considerably among workers, with slower rates of those with clearance also having slower reaction times⁸. A similar result was reported by Jegaden *et al.* in 30 styrene-exposed workers

(mean exposed concentration: 22.7 ppm)⁹. On the other hand, neither Fallas *et al.*⁶, Schoenhuber *et al.* (n=55, 25 ppm)¹⁰, nor Edling *et al.* (n=20, mean exposed concentration: 8.6 ppm)¹¹ reported any significant differences in the simple reaction test results between styrene-exposed workers and controls.

Perceptual motor speed function

With regard to perceptual motor speed function, Letz *et al.* reported that there was a statistically significant relationship between post-shift performance on the digit symbol tests and urinary mandelic acid concentrations of 105 styrene-exposed workers (mean exposed concentration: 29.9 ppm)¹². On the other hand, neither Flodin *et al.*⁵, Fallas *et al.*⁶, Schoenhuber *et al.*¹⁰, Edling *et al.*¹¹, or Yokoyama *et al.* (n=11, 26 ppm)¹³ reported any significant differences

in digit symbol scores between styrene-exposed workers and controls.

Memory and cognition

The Benton visual retention test and digit span test are often used for evaluating memory function. Fallas *et al.* performed the Benton visual retention and digit span tests and reported that no significant differences were found between styrene-exposed groups and controls in either test⁶. Similar results were also reported by Flodin *et al.*⁵. However, Jegaden *et al.* reported that digit span scores achieved by exposed workers were significantly worse than those of the age-matched controls⁹. Schoenhuber *et al.* also performed a digit span (forward) test and reported that those subjects with higher levels of styrene exposure (>700 mg/l PGA + MA) showed a significant impairment in short-term memory¹⁰. Mutti *et al.* evaluated long-term verbal memory function using a logic memory test and showed that logic memory scores were significantly reduced in workers whose urinary mandelic acid and phenylglyoxylic acid concentrations were higher than 300 mmol/mol creatinine, corresponding to an exposure level of more than 50 ppm of styrene in air¹⁴.

Jegaden *et al.* performed a choice reaction time test to evaluate cognition function and reported that exposed groups always showed significantly longer reaction times than did control groups⁹. Furthermore, Mutti *et al.* reported that visual-spatial cognition function, as evaluated by using block design test, was significantly affected in high-exposed workers (exposure levels: >50 ppm)¹⁴. Flodin *et al.*, however, reported no significant differences in memory and cognition between styrene-exposed workers and controls⁵.

Personality and mood

Yokoyama *et al.* performed the Maudsley Personality Inventory (MPI) to evaluate differences in personality between styrene-exposed workers and controls and reported no significant inter-group differences¹³. Cherry *et al.* examined the mood of styrene-exposed workers and reported that exposed workers were much more likely than to report feeling unduly tired than were the controls⁷.

The Effects of Styrene on Color Vision

Results of previous studies

In the recent years, many studies have been carried out on the impairment of color vision. The results of these studies showed that such impairment often occurred among the workers exposed to styrene (Table 4). The interrelationship

between the degree of exposure to styrene and the impairment of color vision was investigated^{6,15-19}. The previous threshold limit of exposure to styrene was 50 ppm in the U.S.A. (until 1997) and Japan (until 1999). However, even exposure to concentrations lower than this limit, might lead to the impairment of color vision^{15, 17, 18}. Some researchers examined the dose response, and found that styrene could induce dose-dependent color vision loss^{15, 16, 18}. It is also confirmed that the impairment of color vision was usually irreversible. No recovery was observed in the tested workers whose exposure to styrene was ceased for one month^{15, 16}. However, recently some recovery was observed among workers exposed to lower levels of styrene.

From our recent study

There are relatively few studies on the relevance of urinary metabolites, recognized biological indicators of styrene exposure, to the investigation of the threshold effects of chronic low-level occupational exposure to styrene. Therefore, we surveyed the loss of color vision among 105 workers exposed to styrene and examined the relation between the concentration of urinary mandelic acid and the CCI of the styrene-exposed group.

Color vision was assessed using the color arrangement test. The most sensitive standard test is the Lanthony desaturated panel D-15 test, in which 15 pastel caps, numbered on the back, were placed in front of the subject in random order. The subject was then required to place the caps in an oblong box, in order of chromatic similarity, starting from a fixed reference cap. Color vision test performance was then assessed categorically and quantitatively. Color vision categories were; (a) normal color vision (no errors, single sequential error or paired reversal), and (b) two or more errors (with subcategorisation according to the relative predominance of errors in red-green or blue-yellow)²⁰⁻²². Quantitative evaluation was performed by calculating the sum of the color differences of the caps placed next to one another (total color difference score: TCDS), with the formula proposed by Bowman²¹⁻²³. The color confusion index (CCI) was obtained when the actual TCDS for a subject's test cap arrangement was divided by the TCDS for a perfect arrangement of that test²²⁻²⁴. Therefore 1 indicated a perfect score and values >1 indicated an increasing loss of color vision.

Because significant linear correlations were present for age and CCI in both workers exposed to styrene ($\gamma=0.43$; $P<0.001$) and controls ($\gamma=0.37$; $P<0.001$), we matched the two groups according to age (within 3 years) to exclude the influence of age. We thus obtained a total of 87 age-matched

Table 4. A review of literatures on color vision loss among styrene workers

Authors (year, country)	Exposure groups (number) (mean age (years))	Period of exposure (range)	Exposure concentration		Results
			External airborn styrene levels (range)	Internal urinary styrene (range) urinary MA (range) urinary PGA (range)	
Gobba <i>et al.</i> (1991, Italy)	7 fiberglass reinforced plastics factories (n=73) (32.0)	84 months (1-324)	16.2 ppm (3.2-549.7)	49.5 ug/l (1.6-202.0) 342.9 mg/l (15.1-3002.0) (-)	1) A significant increase in CCI was seen in the group over 40 years old, when compared with those of controls. 2) A significant difference in CCI ($p<0.01$) between subjects and age-matched controls was observed. 3) Workers exposed to airborne levels exceeding 215 mg/m ³ showed increased CCI than lower exposed-workers ($P<0.05$). 4) Significant linear correlation between urinary styrene and CCI ($r=0.27$, $P=0.02$). Similar correlation was demonstrable for airborne styrene, but not for MA level in urine. 5) After 1 month holiday, CCI values were significantly elevated compared with controls, and no tendency toward a restoration of color vision was observed.
Fallas <i>et al.</i> (1992, France)	ship building (FRP) (60 age-matched pairs) (29.5)	6.5 years (1-29)	24.3 ppm (highest peak: 496.0)	(-) 230 mg/g creat. (2.0-140.0) 57.4 mg/g creat. (0.4-421.2)	1) A significant difference in CCI ($p<0.01$) between subjects and age-matched controls was observed. 2) The differences were found in the blue yellow and/or red-green ranges ($P<0.05$).
Gobba <i>et al.</i> (1993, Italy)	fiberglass-reinforced plastics factory (group 1: n=75, 37.6) (group 2: n=36) (subgroup: n=39, 35.4)	(-)	group 2: 68.2 mg/m ³	group 2: 41.4 ug/l (-) (-)	1) In group 2: Dose related color vision impairment was observed. 2) A significant correlation between environmental styrene and urinary MA was observed. 3) The subgroup was tested just before the summer holiday and then on the first working day one month later, before exposure to styrene. CCI at the renewal of activity (1.20, $SD=0.21$) was not significantly improved over that measured before the holiday.
Chia <i>et al.</i> (1994, Singapore)	FRP boat manufacturing plant (n=21) (43.7)	18.8 years (5-23)	6.0 ppm (1994) 11.0 ppm (2.0-30.0) (1991) 9.7 ppm (2.8-27.7) (1980)	(-) 84.0 mg/g creat. (1.3-297.4) 66.0 mg/g creat. (0.3-1.9)	1) After age matching, significant differences were found in CCI between subjects and controls ($P<0.0006$). 2) No significant linear correlations were present between TCDS and the urinary concentration of MA or PGA.
Eguchi <i>et al.</i> (1995, Japan)	FRP factories (n=64) (38.0)	7 years (0.2-26.8)	18.5 ppm (6.6-36.4)	(-) 0.22 g/l (-)	1) After age matching, significant differences were found in CCI between subject and control ($P<0.01$). 2) CCI was significantly increased in workers with urinary concentration of MA of more than 0.42 g/l compared with workers with lower MA values.
Compagna <i>et al.</i> (1995, France)	reinforced plastic plants (n=79) (29.0)	5 years	205.8 mg/m ³	(-) 0.36 mmol/mmol creat. (-)	1) There was a significant difference in exposure between mask users and non-users ($r=0.95$, $P<0.001$). 2) Significant positive relations were found between internal and external styrene exposure measurements and color vision loss adjusted for age, alcohol consumption, and seniority using a multiple regression analysis.

FRP: fiberglass reinforced plastics, CCI: color confusion index, TCDS: total color difference score, MA: mandelic acid, PGA: phenyl guloxyllic acid, creat.: creatinine, (-): not measured.

pairs. There was a significant difference in CCI between exposed workers and controls (Wilcoxon signed rank test, $p < 0.01$).

To explore the possibility of a dose-effect relation between styrene exposure and loss of color vision, we divided the exposed workers into 3 subgroups according to whether the urinary concentration of mandelic acid was lower than 0.1 g/l (subgroup A), which is equivalent to an atmospheric styrene concentration of about 8 ppm; between 0.1 and 0.2 g/l (subgroup B), which is equivalent to an atmospheric styrene concentration of about 8 to 16 ppm; or greater than 0.2 g/l (subgroup C), which is equivalent to an atmospheric styrene concentration of about 16 ppm or more. Each subgroup was then compared with age-matched controls. There was a significant difference in subgroups B and C, but not in subgroup A (Wilcoxon signed rank test; the p values were < 0.05 , < 0.01 and > 0.05 , respectively). Because of the small difference in CCI among the 3 subgroups (probably

due to age differences among the 3 subgroups; i.e., those in subgroup A were older than those in subgroup C, there were no significant inter-group differences observed by either analysis of variance or the Kruskal-Wallis test (Table 5).

However, the results of stepwise regression analysis clearly showed that CCI had a significant positive relation to urinary mandelic acid after control for age. There was no significant relation between duration of exposure and CCI. Alcohol consumption was found to be not related to CCI, but smoking was negatively related to CCI. No significant relation between age and urinary mandelic acid level was found (Table 6).

Conclusions

Recently, the occurrence of typical occupational disease and intoxication cases caused by industrial chemicals are decreasing due to improvements in the working environment. In addition, it has become more important to take preventive measures against occupational disease by monitoring the working environment and evaluating its effects on the health of workers. It is desirable to evaluate health effects epidemiologically by using both exposure measurements and sensitive indicators such as we mentioned above and to improve industrial workers health.

In future, scientists and policy makers need to obtain the health effects data considering some subjects as follows. First, health effects data must be accompanied with the long-term and accurate exposure measurement. Second, the study must be designed to be able to discriminate the acute and chronic exposure effects. Third, follow-up survey is needed for evaluating whether the effect is reversible or not. Fourth, taking account of age and educational history into the analysis of data is necessary because these confounding factors correlate much to neurobehavioral function. Fifth, molecular-biological approach should be incorporated into risk

Table 5. Age-matched comparison of workers exposed to styrene and controls stratified by urinary mandelic acid concentration

	CCI	Age (years)
Subgroup A (MA: < 0.1 g/l)		
Exposed (n=21)	1.21 (0.26)	39.9 (11.7)
Control (n=21)	1.17 (0.19)	39.2 (11.9)
Subgroup B (MA: 0.1–0.2g/l)		
Exposed (n=24)	1.23 (0.20)	37.8 (12.4)
Control (n=24)	1.12 (0.12)*	37.8 (11.6)
Subgroup C (MA: > 0.2 g/l)		
Exposed (n=42)	1.27 (0.27)	34.9 (11.4)
Control (n=42)	1.13 (0.14)**	34.8 (10.8)

Values are the arithmetic mean (SD). * $p < 0.05$, ** $p < 0.01$; difference between exposed workers and controls with ANOVA. CCI: color confusion index, MA: urinary mandelic acid.

Table 6. Results of multiple regression analysis; (105 workers exposed to styrene)

	Coefficients	SE	Standardised coefficients	p value
Intercept	0.99	0.08	0.99	< 0.001
Age (years)	0.01	0	0.37	< 0.001
MA (g/l)	0.16	0.04	0.34	< 0.001
Exposure duration (years)				n.s.
Alcohol consumption (ml/week)				n.s.
Education attainment (years)				n.s.
Smoking (cigarettes/week)	- 0.01	0	- 0.21	< 0.05

MA: urinary mandelic acid, n.s.: not significant.

Adjusted R² = 0.27

evaluation connected for drug metabolizing enzyme and the metabolizing system of neurotransmitters and so on. For the last, the development of more sensitive biological markers and the improvement of neurobehavioral tests must be important.

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