

Evaluation of Blink Reflex Results Obtained From Workers Previously Diagnosed With Solvent-Induced Toxic Encephalopathy

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We reviewed blink reflexes recorded from 51 railroad workers with long-term occupational exposure to solvents who were diagnosed by others with solvent-induced toxic encephalopathy. No worker fulfilled conventional clinical criteria for dementia or trigeminal mononeuropathy. All workers had normal R1 and R2 blink reflex latencies. R1 latencies correlated significantly with several nerve conduction measures, including F wave latencies, suggesting that some intersubject variability reflected intrinsic conduction properties, not isolated brain-stem function. Although normal, the workers' R1 latencies were significantly prolonged compared with historical control groups, including gender-matched control subjects of similar mean age (11.2 ms vs 9.9 ms; $P < 0.0001$). Stepwise multiple regression models demonstrated significant associations of R1 latency with age and use of CNS-active prescription medications ($P = 0.003$), but duration of occupational solvent exposure did not enter into the models. Paradoxically, workers using CNS-active medications had significantly shorter R1 latencies compared with workers not using such medications (10.9 vs 11.7 ms; $P = 0.01$). Job title, another potential surrogate measure of exposure, was not significantly related to reflex latencies. The geographical site of predominant solvent exposure did influence R1 latency, and workers from one site had longer exposure duration and longer R1 latencies than remaining workers. However, an interaction between age and exposure duration ($r = 0.39$; $P = 0.003$) confounded interpretation of this observation. Disability or work status, mental status findings, or classification of encephalopathy did not influence blink reflex latencies. The overall results do not support, but do not entirely exclude, a possible relationship between subclinical blink reflex abnormalities and occupational exposure to solvents. Nevertheless, it is clear from these results that the small group differences in R1 latency between exposed workers and control subjects are of no diagnostic importance and of uncertain physiologic importance, and they may reflect unrecognized confounders and technical factors. (J Occup Environ Med. 2001;43:713-722)

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Since the initial reports of “painters’ encephalopathy” in the 1970s, the association between occupational exposure to organic solvents and neurologic dysfunction has remained unproven.¹⁻⁸ A primary but unanswered question relates to whether occupational exposure to solvents such as trichloroethylene (TCE) or similar solvents alone or in combination, at low doses and over long periods of time, causes nervous system damage.

Blink reflex studies have been used in attempts to identify objective solvent-induced abnormalities, particularly in relation to TCE exposure.^{9,10} The blink reflex has teleologic protective eye function, producing eyelid closure in response to stimulation of the face or eye. The reflex arc consists of a trigeminal sensory afferent limb, neuronal brain stem relays in the pons and medulla, and a facial nerve efferent motor pathway terminating in facial muscles. The blink reflex can be provoked by several types of stimuli, including percutaneous electrical stimulation of the supraorbital nerve.¹¹ The electrically elicited blink reflex recorded from surface electrodes placed over the orbicularis oculi muscle has two principal components, R1 and R2.^{11,12} The R1 component has the shortest latency and is recorded from the orbicularis oculi muscle ipsilateral to the supraorbital stimulation. The R2 component has a longer latency than the R1 component and is recorded bilaterally following unilateral stimulation (Fig. 1).

The use of blink reflex latencies to evaluate solvent neurotoxicity prob-

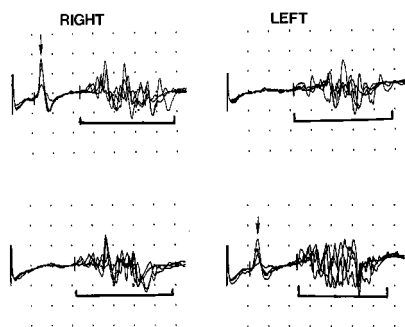


Fig. 1. Representative blink reflexes recorded from the right and left orbicularis oculi muscles of one railroad worker (four superimposed responses) in response to percutaneous electrical stimulation of the right (upper tracings) and left (lower tracings) supraorbital nerves. Ipsilateral R1 responses are indicated by vertical arrows; bilateral R2 responses are indicated by the horizontal bars. Calibration: 200 μ V per division and 200 ms per division. Vertical cross-markings indicate selected R1 and R2 latencies for these tracings.

ably originated with the observation that trigeminal nerve and other cranial nerve dysfunction sometimes occurred after exposure to TCE when used as a general anesthetic.¹³ In this setting, as many as 60,000 patients a year may have been exposed to anesthetic doses of TCE.^{14,15} The syndrome of multiple cranial mononeuropathies was eventually attributed to a decomposition product (dichloroacetylene) resulting from reaction between TCE and soda-lime.^{9,13,16–18} However, the syndrome of multiple cranial mononeuropathies associated with TCE exposure was not limited to anesthetic use.^{18–21} Feldman et al described a patient who was accidentally exposed to TCE vapor while working in a confined space.^{9,22–24} Following the acute onset of lethargy, confusion, and stupor, this patient developed evidence of multiple cranial mononeuropathies. Trigeminal dysfunction was characterized by facial and corneal anesthesia and masseter weakness. Involvement of other cranial nerves produced constricted visual fields, unilateral paresis of accommodation, impaired eye movement, asymmetric ptosis, and facial weakness. Over an 18-month

period of time, most abnormalities improved, but facial hypalgesia and blink reflex abnormalities were present almost 20 years later.^{23,25}

Less well established is the relationship between chronic, low-level occupational or environmental solvent exposure and blink reflex abnormalities. Feldman et al used blink reflex latencies to document the effects of occupational TCE exposure on trigeminal nerve function.²⁶ In one evaluation, blink reflex results obtained from 18 subjects with occupational TCE exposure were compared with control values. They found that subjects with the heaviest exposures had the most prolonged R1 latencies, suggesting that blink reflex measures had application in assessing TCE-induced neurotoxicity.²⁶ Results have been mixed across studies. Ruijten et al evaluated 31 printers with long-term occupational exposure to TCE at threshold limit values.²⁷ They found a slight increase in the masseter reflex latencies in exposed workers compared with control values, but they found no group differences for blink reflex latencies.

Feldman and associates also reported blink reflex results obtained from subjects with chronic low-level TCE exposure through their well water.¹⁰ Only 2 of 21 subjects from this population had abnormal R1 latencies, but there was a highly significant ($P < 0.0001$) difference in the mean R1 blink reflex latency compared with their control values. This difference was attributed to a subclinical effect of chronic, environmental exposure to TCE on trigeminal function.¹⁰

We previously reported our experience with a population of railroad workers with occupational solvent exposure who we had evaluated in the context of litigation.^{7,28} All had been diagnosed previously with toxic encephalopathy by either a neurologist or occupational medicine physician. On the basis of the descriptions of previous examiners, these workers were thought to be representative of railroad workers with solvent-induced encephalopathy. In previous evaluations of some of the same workers reported

here, we found no objective evidence of unexplained polyneuropathy, encephalopathy, or any other uniform syndrome among these workers. The evidence further suggested that most complaints were explained by neuropsychologic factors or other conditions unrelated to occupational solvent exposure. Nevertheless, blink reflexes could be sensitive indicators of subclinical solvent neurotoxicity.^{24,26,29} In the context of testing this hypothesis, the railroad workers we evaluated are of interest because they were described by others as having characteristic findings of solvent-induced encephalopathy in association with particularly high solvent exposures.⁶ We now report the results of blink reflex evaluations among this group of railroad workers.

Methods

Worker Selection and Characteristics

The study was approved by the University of Michigan Medical School Institutional Review Board, and the study sample has been described previously.⁷ Before the analyses, information linking any individual to the data was removed, and data for a random subset of workers were deleted to provide additional anonymity. Blink reflex results for one worker were unavailable for review, leaving information from 51 workers in the final data. The resultant group consists of railroad workers referred to us over approximately 5 years by defense attorneys for independent medical examinations. All workers were involved in litigation against their employer because of alleged occupational solvent exposure producing toxic encephalopathy, and all knew that the examinations were performed in the context of their litigation. Each had a previous diagnosis of toxic encephalopathy, usually using the World Health Organization (WHO) classification of encephalopathy.³⁰ For workers whose type of encephalopathy was not specified by their physician, we applied the WHO terminology. The distribution of

TABLE 1Characteristics of the Railroad Workers (*n* = 51) at the Time of Evaluation

Characteristic	Mean	Range
Age (yr)	50	37–65
Male (<i>n</i>)	49	
Height (M)	1.8	1.6–1.9
Weight (kg)	88.1	58.9–136.0
Body mass index (kg/m ²)	27.8	20.3–37.8
Education (yr)	11.6	6–14
Education < 12 years (<i>n</i>)	13	
Job description (<i>n</i>)		
Machinist	18	
Electrician	15	
Laborer (attendant, carpenter, equipment operator, maintenance)	11	
Pipefitter or boiler maker	7	
Exposure history		
Duration of exposure (yr)	22	10–39
Duration of exposure opportunity (yr)	15	6–35
Time to symptom onset (yr)	16	1–43
Currently working for railroad (<i>n</i>)	19	
Solvent-related work disability (<i>n</i>)	22	

workers based on encephalopathy type included: type 1 (the mildest form of encephalopathy, based on symptoms, not necessarily specific though usually referable to the central nervous system, *n* = 10); type 2A (sustained change in mood or personality change, *n* = 21); type 2B (intellectual impairment on neuropsychologic testing, *n* = 8); type 2A, B (coexisting type 2A and 2B, *n* = 12); and type 3 (severe toxic encephalopathy with features of a chronic dementia, *n* = 0). Complaints attributed to encephalopathy included abnormal memory, impaired mood, poor balance, and headache.

The characteristics of the group are shown in Table 1. Workers were assigned the job classification that reflected their primary assignment during the period of highest exposure. The different job classifications provided different exposure opportunities, although exposure experiences were superficially similar because of common work environments. The common or trade names typically described the chemicals used. Those most frequently reported were TCE, trichlorethane, or perchloroethylene, alone or, more often, in combination. Each worker also was assigned to one of four geographic sites where they had spent the longest period of potential exposure. The sites

consisted of three distinct geographical locations where major railroad yards were located, plus an additional site ("site" D) made of many disparate locations, and each comprised of a small number of workers. The geographic sites possibly provided additional exposure opportunities if there had been different regional practices related to the occupational use of solvents within the railroad industry.

Exposure information was historical, based on the individual worker's description, and verified by review of occupational records when available. The duration of occupational solvent exposure averaged 22 years (range, 10 to 39 years), and all workers reported exposures of at least 10 years duration, partially fulfilling criteria for long-term exposure as reported by others.³¹ The highest-level exposures occurred before the mid-1980s, after which exposure was minimal because of changing work practices. The opportunity for solvent exposure based on the presence of solvents in the workplace therefore differed from that reported, averaging 7 years less. Based on this calculation, 43 workers still fulfilled the duration criteria for long-term exposure. All workers regularly experienced symptoms at work that they attributed to acute solvent intoxication,

including transient headache, dizziness or lightheadedness, "drunkenness," and balance problems. No worker reported accidents, injuries, or loss of consciousness related to acute solvent intoxication. No worker complained of facial numbness, jaw closure weakness, or other symptoms suggestive of unexplained isolated cranial neuropathy.

A clinical neurologic examination had been performed on all workers, as described in previous reports.^{7,28} The examination included review of medical and occupational histories. In addition to the history provided by the worker, medical records were reviewed to confirm the presence of medical conditions that could adversely affect the nervous system. The systemic diagnoses established by treating physicians were accepted as accurate.

Previous test results including magnetic resonance imaging and electroencephalographic reports also were reviewed. According to these reviews, several workers had conditions unrelated to solvent exposure that could influence blink reflex studies. These potentially confounding conditions included adult-onset diabetes mellitus (3); high blood pressure (17); liver disease (1); chronic pain other than headache (10); and prior alcohol abuse (self-report or historical record) (6), with one of these six reporting prior polysubstance abuse. Thirty-one workers were using prescription medications with potential CNS-effects, including antidepressant (23), anxiolytic (6), combined antidepressant and anxiolytic (4), narcotic analgesic (4), and stimulant (2) medications. Thirty-two workers were receiving a variety of other medications without direct CNS effects. Included were antihypertensive, anticholesterol, antidiabetic, cardiac, cardiovascular, corticosteroid, and headache medications. Thirteen workers were using no prescription medications at the time of our evaluation; three of these previously had taken antidepressant medications.

Information from historical records indicated that 39 workers had conventional electroencephalographic examinations performed previously. All were normal. Forty-eight workers had cranial magnetic resonance imaging studies. Eight of the 48 studies were abnormal, but only one demonstrated cerebral atrophy, described as mild or equivocal. The other seven abnormal magnetic resonance imaging studies demonstrated evidence suggestive of scattered ischemic lesions. These included two workers with diabetes mellitus, four with elevated blood pressure (three diagnosed with and treated for hypertension), and one with vascular disease.

Neurologic Evaluation

A standard clinical neurologic examination was performed on all workers.³ This included a detailed cranial nerve examination. Medical records were reviewed to confirm the presence of medical conditions that could adversely affect the nervous system. Previous medical examinations and laboratory results including magnetic resonance imaging and electroencephalographic reports were reviewed. The neurologic examination included a structured mental status examination, and a Mini-Mental State Examination score was calculated for each worker.³² Several definitions of "encephalopathy" were used, including the one developed at the 1985 WHO solvent conference.^{2,30} Because of the limitations of the WHO criteria, including reliance on nonspecific symptoms and failure to incorporate neurologic findings in the definition of encephalopathy, we also assigned a traditional definition of encephalopathy (clinically evident encephalopathy) based on symptoms and neurologic signs of impairment. Clinically evident encephalopathy required the presence of appropriate symptoms (memory loss, impaired cognition, irritability, short attention span, or impaired behavior) and mental status and motor/reflex examination abnormalities.⁷ Abnormal mental status

testing required disturbance of two or more of the following: personal orientation to self and environment, simple calculations, short-term memory, digit span, comprehension, similarity testing, multiple step command, or an abnormal Mini-Mental State Examination summary score. An abnormal motor/reflex examination required two or more of the following: postural tremor, slowed coordination, abnormal alternate motion rate, asterixis, dysarthria, akathisia, ataxia, increased tone, increased muscle stretch reflexes, primitive reflexes, or myoclonus.

Nerve Conduction Studies

Sensory and motor nerve conduction results were reviewed from unilateral sural, peroneal motor, median sensory and motor, and ulnar sensory nerves, as reported previously.²⁸ Standard techniques of supramaximal percutaneous nerve stimulation and surface recording were used, based on anatomic landmarks and standardized stimulation to recording electrode distances.^{33,34} Skin temperatures were monitored at the palm and at the calf between stimulating and recording electrodes using an analog thermometer. Temperature was monitored and limbs warmed above 31°C using moist heat placed over the forearm or calf if necessary.

Blink Reflex Studies

Bilateral blink reflexes had been recorded from the orbicularis oculi muscles bilaterally using surface electrodes in response to percutaneous electrical stimulation of the right and left supraorbital nerve.¹² Response measures included ipsilateral R1 latency and ipsilateral and contralateral R2 latencies. The individual latency recorded was taken as the shortest reproducible latency measured from four to eight acceptable responses. A uniform stimulation protocol delivered stimuli randomly at intervals of 5 to 15 seconds without cueing to reduce anticipation. The electromyographer visually examined each tracing as it was recorded. Tracings contaminated by

excessive baseline noise, such as associated with volitional or inadvertent orbicularis oculi activation or other movement unrelated to supraorbital nerve stimulation were excluded, and the trial was repeated. Representative blink reflexes recorded from one worker are shown in Fig. 1.

Statistical Analysis

The frequency of individual blink reflex abnormalities was tabulated, and average blink reflex measures for the group were calculated. Blink reflex results were compared with those of several historical control groups. The control groups included the University of Michigan adult upper limit of normal values used to distinguish normal from abnormal studies³⁵; published upper limits of normal using similar technique^{12,36}; and results obtained from asymptomatic, neurologically intact control subjects who were matched by gender to the study workers and of similar mean age.³⁷ Because there were no significant side-to-side differences in any of the blink response measures, all R1 and R2 latency comparisons were made using data obtained from the right-side stimulation. Blink reflex latencies demonstrated relatively symmetric distributions. Student *t* test comparisons were made using a *P* value of 0.05 to identify statistical significance. Potential differences in blink reflex latencies among workers with different WHO classification of encephalopathy were examined using analysis of variance (ANOVA) models.

Stepwise multiple linear regression models were used to identify the contribution of demographic variables (eg, age, education); potentially confounding variables (history of alcohol abuse, and use of CNS-active medications); and exposure duration on blink reflex latencies. The significance level for including a term was $P < 0.05$ and for removing a term, $P > 0.10$. Correlations between continuous variables were assessed using Pearson's coefficients, and nonparametric correlations were

assessed with Spearman's coefficients. Potential differences in exposure duration (reported and based on exposure opportunity) and blink reflex latencies, between workers in different job categories based on job title or different geographical work locations during the time of predominant exposure, were examined using ANOVA models.

Results

Cranial nerve abnormalities identified on neurologic examination included one worker each with retinopathy (in a worker with diabetes mellitus), anisocoria, and a tonic (Adie's) pupil. An additional worker who had facial asymmetry had no evidence of facial muscle weakness. No worker had findings suggestive of a trigeminal mononeuropathy. Specifically, all workers had normal facial sensation (touch or pin) and normal masseter strength, including seven workers with symmetric sensory loss and five workers with focal extremity sensory abnormalities.

Six workers fulfilled the clinical criteria for mild sensorimotor polyneuropathy based on appropriate clinical symptoms and signs (symmetrical sensory loss or absent ankle reflexes). Three of the six fulfilled electrodiagnostic criteria for confirmed polyneuropathy. Two of the three workers with confirmed polyneuropathy had diabetes mellitus, and their nerve conduction findings were consistent with diabetic polyneuropathy. The third worker had findings characteristic of a diabetic membranopathy and also had a family history of diabetes, but had never been evaluated for diabetes. The remaining three workers had no electrodiagnostic evidence of polyneuropathy.

The results of the bilateral blink reflex recordings obtained from the 51 solvent-exposed railroad workers are shown in Table 2. The distribution of right R1 and bilateral R2 blink reflex latencies recorded in response to right supraorbital nerve stimulation demonstrated a normal distribution. No worker had abnor-

TABLE 2

Results of Bilateral Blink Reflex Recordings Obtained From Solvent-Exposed Railroad Workers ($n = 51$)

Measure	Solvent-Exposed	
	mean + SD	Range
R1 (ms)		
Right R1	11.2 + 1.06	9.0–13.6
R1 > 13 ms (n)	2/51	
R1 > 14 ms (n)	0	
Left R1	11.3 + 1.09	8.8–14.0
R1 > 13 ms (n)	3/51	
R1 > 14 ms (n)	0	
Right-left	-0.04 + 0.42	-1.0–1.3
Right-left > 1.5 ms (n)	0	
Ipsilateral R2 (ms)		
Stimulate right, record right	32.2 + 2.98	26.0–38.7
R2 > 41 ms (n)	0	
Stimulate left, record left	32.3 + 3.19	24.6–38.7
R2 > 41 ms (n)	0	
Right-left	-0.1 + 1.50	-3.7–3.1
Right R2-left R2 > 8 ms (n)	0	
Right R2-left R2 > 3 ms (n)	2/51	
Contralateral R2 (ms)		
Stimulate right, record left	32.4 + 3.14	26.3–39.7
Contralateral R2 > 41 ms (n)	0	
Stimulate left, record right	32.7 + 3.26	26.0–39.8
Contralateral R2 > 41 ms (n)	0	
Right-left	-0.26 + 1.42	-3.7–2.8
Ipsilateral R2-Contralateral R2		
Stimulate right	-0.23 + 1.07	-3.7–2.1
Stimulate left	0.36 + 1.19	-3.4–2.8
Right-left	0.14 + 1.41	-3.8–3.1
Right-left	0.14 + 1.41	
Ipsilateral R2-contralateral R2 > 5 ms (n)	0	
Ipsilateral R2-contralateral R2 > 3 ms (n)	3/102	

mal blink reflex studies, based on the absolute upper limits of normal for R1, ipsilateral R2, or contralateral R2 latency values used clinically in the University of Michigan electromyography laboratory for the past 20 years. Four workers had borderline-prolonged R1 latencies exceeding 13 ms (bilateral in one worker and unilateral in three workers). The worker with bilateral borderline-prolonged R1 latencies had diabetes mellitus. One of the three remaining workers had a family history of diabetes and nerve conduction findings characteristic of a diabetic membranopathy, but he had never been evaluated for diabetes. These four workers with borderline-abnormal R1 latencies were older than were remaining workers (59 vs 50 years; $P = 0.0028$) and demonstrated similar

borderline abnormalities on nerve conduction studies. For example, they had longer median and peroneal F wave latencies (respectively: 33.2 vs 29.0 ms; $P = 0.0021$ and 61.5 vs 51.4 ms; $P = 0.0002$), slower median and peroneal conduction velocities (respectively: 46 vs 55 M/s; $P = 0.0001$ and 39 vs 45 M/s; $P = 0.003$), and smaller sural amplitudes (6.3 vs 13.3 μ V; $P = 0.024$) compared with remaining workers. These results suggest that the borderline-abnormal R1 latencies reflected a component of an overall generalized process, not a focal brain-stem abnormality. No significant side-to-side differences for R1 or R2 latencies were identified.

Several nerve conduction measures correlated significantly with R1 latency, but few measures correlated sig-

TABLE 3

Comparison of Blink-Reflex Results Obtained From Solvent-Exposed Railroad Workers ($n = 51$) With Historical Control Groups, Including Age and Anthropometric Data, When Available

Measure	Healthy Controls (mean + SD, $n = 83$)*	Solvent-Exposed (mean + SE, $n = 51$)	Gender-Matched (mean + SE, $n = 25$)†	P Value (solvent- exposed vs gender-matched)‡
Age (yr)	37	50 ± 6.2	50 ± 10.8	0.9818
Height (M)		1.8 ± 0.06	1.8 ± 0.09	0.4002
Weight (kg)		88.2 ± 15.7	85.3 ± 15.5	0.4601
BMI (kg/m ²)		27.8 ± 3.9	27.5 ± 4.8	0.7904
Blink reflex latencies (right-side stimulation)				
R1 (ms)	10.5 ± 0.8	11.2 ± 1.1	9.9 ± 0.9	<0.0001
Ipsilateral R2 (ms)	30.5 ± 3.4	32.2 ± 3.0	31.1 ± 2.9	0.1257
Contralateral R2 (ms)	30.5 ± 4.4	32.4 ± 3.1	32.0 ± 2.9	0.5897

* See Reference 36.

† See Reference 37.

‡ Student's *t* test.

nificantly with ipsilateral R2 or contralateral R2 latencies. Specifically, most measures of conduction speed, particularly as measured by F wave latency, and sural amplitude were directly correlated with R1 latency, with better performance in each being weakly associated. For these correlations, the highest R^2 values ranged from 0.21 (median sensory conduction velocity, median F response latency, and peroneal F response latency) to 0.25 (sural amplitude).

Although all workers had normal blink reflex latencies, mean R1 latencies were longer than historical normal values (Table 3). The mean R1 (averaged for right and left sides) of 10.5 ms ± 0.8 ms (standard deviation) reported by Kimura was obtained from 83 healthy subjects 7 to 86 years of age (mean, 37 years).³⁶ Assuming a symmetrical distribution (a reasonable assumption for R1 latencies), this mean R1 latency is significantly less ($P < 0.01$) than the mean R1 latency of 11.2 ms we found for the 51 workers. However, the workers were substantially older than the healthy subjects (50 vs 37 years), and R1 latency (like many other conduction measures) increases with age. Based on the R1 latency-age regression line slope of 0.023 ms/year derived for normal subjects,³⁷ the age-corrected control R1 latency of 11.1 ms no longer

differs significantly from the mean R1 latency obtained for the 51 workers. However, comparison with a group of gender-matched control subjects of similar mean age (50 years in both groups) continued to demonstrate a significant difference in R1 latencies, with the matched control subjects having a mean R1 latency more than 1 ms shorter than the workers with a previous diagnosis of toxic encephalopathy (9.9 vs 11.2 ms; $P < 0.0001$). Based on this same comparison group, no significant differences were found for ipsilateral or contralateral R2 latencies. There also were no significant differences in R1 ($P = 0.54$), ipsilateral R2 ($P = 0.25$), or contralateral R2 ($P = 0.47$) latencies among workers classified as having WHO type 1, 2A, 2B, or 2A, B encephalopathy.

Stepwise multiple linear regression models were generated to examine the relationship between measured blink reflex latencies and estimated duration of exposure, while controlling for the possible confounding effects of age, educational level, height, weight, body mass index, current mental status performance (Mini-Mental State Examination score), possible depression (self-report or historical record), history of alcohol abuse, and current use of CNS-active medications (Table 4). Stepwise linear regression analysis indicated that the R1 latency was signif-

icantly associated with age and the current use of CNS-active medications ($P = 0.003$), and these two variables accounted for 18% of the total variance in R1 performance. In this model, younger age and current use of CNS-active medications were both associated with decreasing R1 latency. Although exposure duration demonstrated a significant relationship to R1 latency ($r = 0.34$; $P < 0.01$), there was also a significant interaction between age and exposure duration ($r = 0.39$; $P = 0.003$) (Table 5). In regression analyses, age was the stronger predictor and exposure duration did not add any additional explanatory power. No other explanatory variables entered the model. Linear regression analyses for ipsilateral and contralateral R2 latencies revealed no significant relationships with exposure duration or any other potentially confounding variables.

The potential influence of job title and geographical location during the time of predominant exposure were compared in terms of blink reflexes with ANOVA models. There were no significant differences between workers with different job titles and R1 ($F(3,47) = 0.28$, $P = 0.84$), ipsilateral R2 ($F(3,47) = 0.37$, $P = 0.77$), or contralateral R2 ($F(3,46) = 0.21$, $P = 0.89$) latencies. Workers from one site (site C) exhibited, on average, longer R1 latencies than

TABLE 4

Stepwise Multiple Linear Regression Models Used to Evaluate Significant Associations With Measured R1 Blink Reflex Latency

Dependent Variable	Independent Variables	Adjusted R ²	Beta/Partial Correlation	P Value
R1		0.183		0.003
	<i>Variables in the equation</i>			
	Age		0.32	0.02
	CNS-active medications		-0.27	0.05
	<i>Variables not in the equation</i>			
	Working status		0.22	0.12
	Exposure duration		0.20	0.18
	Height		0.18	0.21
	Weight		0.08	0.57
	Mental status score		-0.08	0.58
	Possible depression		-0.08	0.60
	History of alcohol abuse		-0.01	0.97
	Body mass index		-0.003	0.98

workers from one of the remaining three sites (site D; 11.9 vs 10.6 ms; $F(3,47) = 4.34$, $P = 0.009$). Further, workers from different geographical sites experienced significant differences in exposure duration ($F(93,48) = 4.49$, $P = 0.007$). In particular, workers at site C had a significantly longer period of potential exposure (27 years) than workers at two of the remaining three sites (sites B or D; 20 and 19 years, respectively). However, this observation of differences in R1 latency between workers from site C and site D is complicated by differences in age. Namely, workers from site C were significantly older than workers from site D ($F(3,47) = 4.40$, $P = 0.008$), and age was significantly correlated with R1 latency ($r = 0.39$, $P = 0.003$). There were no significant differences between workers in different geographical areas and the ipsilateral or contralateral R2 latencies ($F(3,47) = 1.03$, $P = 0.39$; ($F(3,46) = 2.05$, $P = 0.12$, respectively).

Discussion

No absolute blink reflex R1 or R2 latency abnormalities were detected among this group of workers, who were diagnosed by others as having toxic encephalopathy due to occupational solvent exposure. Several possibilities exist to explain these find-

ings: (1) the blink reflex measures might be insensitive for use among individual subjects for diagnosing chronic solvent-induced toxic encephalopathy; (2) the workers might not have toxic encephalopathy; or (3) previously existing blink reflex abnormalities might have resolved, or at least improved, so that all values are now in the normal range. The significant positive correlations (all representing better performance) between R1 latencies and several measures of nerve conduction velocity, particularly sural amplitude and F wave latencies, suggest that some of the intersubject variability reflects intrinsic conduction properties, not isolated brain-stem function. The paucity of significant correlations between measures of nerve conduction and R2 latencies probably reflects the greater variability of R2 latencies compared with R1 latencies and most nerve conduction measures. The R2 latency variability is thought to reflect habituation and altered interneuronal excitability in the brain stem, and it accounts for the poor reproducibility of R2 latencies during repeated trials.¹²

Although normal, we did find that the mean R1 latency was significantly longer for this group of workers compared with historic mean R1 latencies reported for healthy subjects.^{12,26,37}

How do the blink reflex results we obtained from railroad workers who had been diagnosed by others as having chronic solvent-induced toxic encephalopathy compare with the results reported for other workers with occupational exposure to solvents, including TCE? The two types of reports available are those related to acute or severe exposures producing clear neurologic impairments, and those related to chronic, low-level occupational or environmental exposures that do not produce overt neurologic signs. The latter consist primarily of selected group comparisons of exposed and control subjects.

The mean R1 blink reflex latencies we found among railroad workers with occupational solvent exposure are substantially less than the values reported for individual workers with acute or severe exposures to solvents producing neurologic impairments. For example, the patient with an acute TCE exposure reported by Leandri et al had R1 latencies that ranged from 16.4 to 18.6 ms.¹⁹ Similarly, the patient with complete facial anesthesia and residual blink reflex abnormalities almost 20 years after TCE exposure reported by Feldman et al had R1 latencies 12.7 and 14.0 ms.²⁶ None of the railroad workers we evaluated had R1 latencies exceeding 14 ms, but a few had R1 latencies exceeding 12.7 ms. Feldman also reported blink reflex latencies of subjects exposed to various levels of TCE and other neurotoxins.²⁴ The four workers with extensive TCE exposure exceeding 50% of each workday for at least 1 year, or exceeding 15 minutes in a poorly ventilated area, had mean R1 latencies of 3 SD greater than control subjects (mean R1 latency, 13.0 ms; range, 12.7 to 13.2 ms). The mean R1 latency of 13.0 ms for this group of four workers with extensive TCE exposure is substantially greater than the mean value of 11.2 ms we report, but this mean R1 latency for all eight workers reported by Feldman with any occupational TCE exposure is not (11.2 ms vs 11.5; $P = 0.5855$).

TABLE 5

Correlations Among Blink Reflex Latencies (R1 and Ipsilateral and Contralateral R2) and Potential Influences or Confounders*

	Pearson's			Spearman's		
	R1	Ipsi R2	Contra R2	R1	Ipsi R2	Contra R2
Age	0.39**	0.10	0.13			
Education	-0.05	-0.01	-0.02			
Height	0.14	0.16	0.12			
Weight	0.05	-0.04	-0.06			
Body mass	-0.03	-0.13	-0.14			
Exposure years	0.36**	0.15	0.18			
Exposure years to 1987	0.34**	0.13	0.15			
Use of CNS medications				-0.35**	-0.14	-0.17
WHO diagnosis				-0.06	-0.07	-0.14
Possible depression				-0.17	0.02	-0.05
Still working				0.10	-0.04	-0.04
History of alcohol abuse				0.07	0.20	0.19

* Ipsi, ipsilateral; contra, contralateral; CNS, central nervous system; WHO, World Health Organization.

** $P < 0.01$.

Further, comparing both groups with the additional nine subjects reported by Feldman et al, who had a variety of exposure to other neurotoxic chemicals but not TCE, failed to demonstrate statistically significant differences (ANOVA), even though the mean R1 latency for the remaining subjects was close to the normal mean they described (10.7 vs 10.4 ms). This remained true even after excluding an outlying value, in which case the means more closely resemble their normal R1 latency value (10.5 vs 10.4 ms).

Even less striking than the blink reflex abnormalities reported for workers with occupational exposure to TCE are the R1 latency values reported by Feldman et al for persons with environmental TCE exposures.¹⁰ Those investigators found statistically significant increased R1 latencies for 21 subjects chronically exposed to TCE in their well water. However, according to the published distributions of latencies, the mean R1 latency for this group of subjects is about 11.5 ms, slightly longer than the mean R1 latency we report (11.2 ms). The conclusion that significant electrodiagnostic evidence of trigeminal nerve damage based on blink reflex results is more likely to be detected among those intensely exposed to TCE in the indus-

trial setting as compared with those with low-level environmental exposures may be correct, but it remains an unproved hypothesis. Moreover, even the presumption that cross-sectional comparisons demonstrating statistically significant solvent-exposed versus control differences are related to solvent exposure remains uncertain. Difference of the magnitude we report, although statistically significant when compared with available normal values, are of unknown clinical or electrophysiologic significance. Further, none of the workers we examined had any clinical symptoms or signs of trigeminal, brain-stem, or facial nerve dysfunction, and all individual blink reflex measures were within the normal range. This combined information makes inappropriate the notion that the differences are indicative of "damage" to some component of the blink reflex.

Numerous factors influence blink reflex latencies, including the presence of some types of polyneuropathy.^{12,12} For example, the individual among the 51 workers whose studies we reviewed who had the longest R1 latency had diabetes mellitus and evidence of a diabetic polyneuropathy. Diabetes mellitus is one of the systemic disorders associated with prolonged blink reflex latencies,³⁸ presumably attributable to a subclinical membranopathy

involving peripheral and cranial nerves. Patients with peripheral demyelinating disorders, such as chronic inflammatory demyelinating polyneuropathy, have markedly prolonged R1 and R2 latencies, with mean values of 16.4 and 42 ms, respectively.¹² The values reported for such disorders far exceed the small prolongations we found for this group of workers with occupational exposure to solvents. As expected, we found a number of significant correlations between measures of extremity nerve conduction velocity, particularly F wave latencies, and blink reflex latencies. This relationship between peripheral nerve conduction and blink reflex latencies supports the concept that individual characteristics, including age, height, body mass index, and core temperature, contribute to several nerve conduction characteristics in general, explaining in part the well-established intersubject variation among these measures.

Factors affecting blink reflex latencies include not only those factors that also influence peripheral nerve conduction in general, but also technical factors related to subject arousal and activation during testing. Several central nervous system influences on R1 and R2 are known, and such information contributes to our understanding of supratentorial in-

fluences on the blink reflex measures.¹¹ For example, R1 and R2 variation during different sleep stages and during anesthesia suggest that the underlying mechanism includes both supranuclear and infranuclear activities,^{39–42} as does the variation associated with habituation and anticipation.^{11,43,44} Even the degree of orbicularis activation (eg, eyes open-closed) prior to the supraorbital stimuli influences the blink reflex.⁴⁵ It is not surprising, therefore, that minor technical differences between studies may produce minor but statistically significant interstudy differences. It is, in part, for these reasons that evaluation of even well-designed and well-executed cross-sectional studies or selected groups of exposed cases cannot determine the cause for any identified differences, such as those found in this study, that are derived from control subjects comparisons.

The presence of a definite dose-response effect between exposure and blink reflex latencies would support a cause-effect relationship between solvent exposure and prolonged blink reflexes. To date, such evidence is unavailable. Our study, like others, has limited solvent exposure information. Duration of employment in an occupation using solvents is one potential surrogate of overall exposure. However, among the railroad workers we reviewed, most reported long employment performing the same general type of job. Therefore duration of employment was strongly related to worker age, because the older workers had the longest duration of potential exposure. Although increased R1 latency was associated with increased duration of potential exposure, age was a stronger predictor than duration of exposure (increased age, increased R1 latency). Other potential surrogates for exposure, such as primary job classification or type of encephalopathy, revealed no potential dose response relationships. The effect of occupational geographic site on blink reflex latency was evaluated, and the finding that one site had significantly prolonged blink

reflexes compared with one of the remaining three sites remains incompletely explained. Unfortunately, workers at the site with the longest mean R1 latency were significantly older than workers at the remaining site (55 vs 47 years). Further, the remaining “site” actually consisted of several locations, because this group included a number of smaller groups, each comprised of a small number of workers insufficient to qualify as a separate site. Overall, the several evaluations of exposure duration, including job title and geographic site, provided little support for a dose-response effect other than the findings readily explained by an interaction with age.

Although the significant direct influence of age on R1 latency was not surprising (younger age, shorter latency), the influence of current use of CNS-active medications was unanticipated. Together, these two variables accounted for 18% of the total variance in R1 performance. Even after accounting for the effects of age, the use of CNS-medications significantly influenced the R1 latency. Paradoxically, workers who reported current use of CNS-active medications had shorter R1 latencies compared with the remaining workers who were not using such medications (10.9 vs 11.7 ms; $P = 0.0125$). Among the 31 workers using any CNS-active medication at the time of evaluation, primary mood and balance complaints were significantly more prevalent compared with the remaining 20 workers. As expected, most of the medications were prescribed for complaints of depressed mood. The chief complaint of poor balance was confounded by an interaction with use of CNS-active medications, and impaired balance is a common adverse effect of the prescribed medications used by these workers. Our evaluations did not identify other factors influencing blink reflex latencies.

In the present study, it is possible that some yet-unidentified confounder explains the statistically significant but numerically small differences in some

of the reflex measures we found. Resolution of this concern about the role of possible confounders will likely require a masked cohort study with repeat evaluation before and after solvent exposure. What can be concluded from the present evaluation is that railroad workers with reported solvent-induced encephalopathy might have subtle prolongation of R1 latency within the normal range. Nevertheless, the magnitude of the increase is small, and even less than that described for subjects with chronic, low-level environmental exposure to TCE, despite that these railroad workers are felt by some to have perhaps the highest occupational exposures to solvents of any workers in the United States. Our results also included evidence of normal clinical and nerve conduction studies. Although the small prolongation of mean R1 latency among this group of railroad workers with occupation solvent exposure deserves further evaluation, the findings are not cause for concern and do not seem to reflect evidence of a direct neurotoxic effect of the blink reflex arc. In summary, our overall results do not support, but do not entirely exclude, a possible relationship between subclinical blink reflex abnormalities and occupational exposure to solvents. Nevertheless, it is clear from these results that the small group differences in blink reflex latency between exposed workers and control subjects are of no diagnostic importance and of uncertain physiologic importance, and they may reflect unrecognized confounders and technical factors.

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