Peripheral and Central Auditory Dysfunction Induced by Occupational Exposure to Organic Solvents

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Objective: *To examine the effects of solvent exposure on hearing function, through an audiological test battery, in a population not occupationally exposed to high levels of noise.* ***Methods:*** *One hundred ten workers from a coating factory were studied. Jobs at the factory were divided into three different levels of solvent exposure. Hearing status was assessed with a test battery including pure-tone hearing thresholds (0.5–8 kHz), high-frequency hearing thresholds (12 and 16 kHz), and dichotic listening measured through dichotic digits test. Multiple linear regression models were created to explore possible association between solvent exposure and each of the hearing outcomes.* ***Results:*** *Significant associations between solvent exposure and the three hearing outcomes were found. Covariates such as age, gender, race, and ethnicity were also significantly associated with the studied hearing outcomes.* ***Conclusions:*** *Occupational exposure to solvents may induce both peripheral and central auditory dysfunction. The dichotic digits test seems as a sensible tool to detect central auditory dysfunction associated with solvent exposure. Hearing loss prevention programs may use this tool to monitor hearing in solvent-exposed workers.* (J Occup Environ Med. *2009;51:1202–1211*)

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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Work-related hearing loss (HL) due to noise exposure remains a prevalent occupational condition.[1] In addition to noise, other agents such as metals, asphyxiants, pesticides, and organic solvents may be hazardous to human hearing.[2–6] In the occupational health and safety arena, solvents have been associated with dermal effects,[7] neurobehavioral changes,[8] and respiratory effects,[9] among other pathologies. Millions of persons are currently exposed to solvents in their workplaces.[10] One of the first reports on the adverse effects of solvents on human hearing comes from Szulck-Kuberska et al,[11] who studied a group of workers exposed to trichloroethylene. Animal studies have found cochlear damage due to aromatic solvent exposure.[12,13] One of the most studied solvent in animals is toluene. Research has shown that toluene can reach cochlea and induce damage in the outer hair cells.[12,13] Recent studies have also demonstrated that toluene and other solvents may adversely affect the acoustic reflexes due to an anticholinergic effect on the auditory efferent motoneurons.[14,15] Field studies conducted in populations of solvent-exposed workers have found an increment in the prevalence of HL among solvent-exposed workers in comparison with nonexposed control subjects.[16–19] Also, human studies have suggested that due to the neurotoxic effects of solvents, these chemicals may induce dysfunction on the central auditory system.[20–22] Most of these clinical studies used a small number of workers exposed to solvents. In 2002, several laboratories started collaborating under a Commission grant (fifth framework), in a European project called Noisechem. To study the combined effects of noise and solvents on the auditory system, Noisechem proposed the use of an audiological test battery.[23] The approach of a test battery was proposed because of the combined ototoxic and neurotoxic effects of solvents on the auditory system.

In summary, solvent-induced hearing loss (SIHL) is a complex pathological entity that may be originated due to a combination of ototoxicity and neurotoxicity. This is different to the deleterious effects of noise on hearing. Noise exposure mainly affects the outer and inner hair cells in the cochlea,[24–26] whereas solvents can affect both the hair cells and central auditory structures. In experimental animals, the midfrequency region of the cochlea is particularly affected by solvents.[12,27] Considering that the auditory dysfunction associated with solvents is different to that one associated with noise exposure, the test battery used to assess each condition must therefore not be the same.

Taking into consideration the neurotoxic effects of solvents, the auditory effects induced by these chemicals may be more complex than the sole presence of abnormal hearing thresholds. Indeed, a central auditory dysfunction may likely be related to solvent exposure. Therefore, this aspect should be incorporated in the monitoring of exposed workers. However, there is a lack of scientific evidence on which test should be appropriate to assess the central auditory function in solvent-exposed workers. Only a limited number of studies have examined hearing outcomes using other tests to complement data from pure-tone audiometry. Thus, a research gap still remains on the most suitable tests, which should comprise an audiological test battery for solvent-exposed workers.

From the occupational and safety perspective, an appropriate test is the one not only capable of detecting the dysfunction but also suitable to be carried out in the occupational setting as a screening procedure. This means that it is easy to be administered, does not take long time to be completed, and has high validity and reliability. Taking into account this issue, the present research project aimed at incorporating within the hearing test battery for solvent-exposed workers, a test for central auditory function, which can fulfil these criteria. The selected procedure was the dichotic digits (DD) test. This test was first introduced by Kimura,[28] and further research demonstrated that it is a sensitive test to detect central auditory dysfunction.[29]

Materials and Methods

Study Population

Subjects were selected from a factory in New Haven, CT, that manufactures reinforced fabrics. The industrial process in this factory involves application of polyurethane coating on a variety of fabrics to make the fabrics waterproof, weather resistant, and durable and pliable depending on the intended use of the fabric. Approximately 130 employees work in the factory. During the annual surveillance activities in 2006, all workers participating in the examinations ($N = 115$) were invited and agreed to participate in this research study. Ninety-one of these employees are production workers and 24 of them are administrative staff. Five of the 115 workers had middle ear pathology and were therefore excluded from further analysis. Table 1 shows the demographics for the remaining 110 participants included in the final analysis grouped according to solvent exposure level (see later). The study protocols were approved by the Human Investigation Committee of the Yale University School of Medicine.

Exposure Assessment

Toluene and methyl ethyl ketone are used in major quantities but many other solvents including trichloroethylene, acetone, n-methyl pyrrolidone, dimethylformamide, chlorobenzene, and isopropyl alcohol are also regularly used in the factory. These components are mixed in different concentrations depending on the desired production outcome. Workers were, therefore, exposed to different mixtures of solvents over time.

Each job in the factory was reviewed by an industrial hygienist familiar with the industrial processes used and was categorized on a scale from 1 (minimal exposure) to 3 (maximal exposure). Category 1 included administrative assistants, sales assistants, supervisors, receptionists, and office managers. They were lightly exposed to solvents. Category 2 included maintenance engineers, production supervisors, and jobs cutting or inspecting finished fabric who were moderately exposed to solvents. Category 3 included coating machine operators, helpers, mixers, and hazardous waste handlers. They were highly exposed to solvents. The cumulative exposure for each participant was obtained as the multiplicative product of two factors: years at the factory and job category.

Table 2 shows mean airborne concentrations for methyl ethyl ketone and toluene (the solvents used in greatest quantity at the factory) for group 2 and group 3 workers, from samples taken at the factory over the past 20 years.

In addition to solvent exposure, reports of noise levels at the factory over the past 10 years were obtained. Documented noise levels in the plant ranged from 74 to 84 dBA.

Questionnaire

All subjects completed a questionnaire, available in both Spanish and English, related to risk factors for acquired HL. The questionnaire included demographic information as well as questions about self-reported solvent and noise exposures (including episodes of solvent intoxication at work), and medical risk factors for HL.

TABLE 1
Characteristics of the Study Participants

	Group 1 (n = 20)			Group 2 (n = 18)			Group 3 (n = 72)		
Variables	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range
Age (yr)	38.1 (11.6)	40	21–56	41.0 (12.4)	39.5	22–66	39.5 (11.4)	38.5	19–67
Gender									
Female	12			1			4		
Male	8			17			68		
Race									
White	15			12			64		
Others	5			6			8		
Ethnicity									
Hispanic	4			9			58		
Non-Hispanic	16			9			14		
Intoxication	1			2			15		
RNE	4.9 (10.3)	0	0–42	6.0 (8.8)	0.5	0–30	2.9 (6.2)	0	0–30
Tenure	7.4 (4.9)	5.5	1–17	6.3 (6.2)	4.0	1–19	5.71 (5.9)	3.8	0.5–30
Smoking	5.5 (10.3)	0	0–40	3.2 (6.8)	0	0–20	4.8 (8.3)	0	0–37
Alcohol	63.1 (157.5)	0	0–500	24.2 (46.3)	0	0–150	22.7 (64.7)	0	0–315

Means, SD, medians, and range for the covariates for the total group and subgroups of subjects. Values in the parentheses represent standard deviation.

Group 1 includes workers with the lowest solvent exposure; group 2, workers with moderate solvent exposure; group 3, workers with the highest solvent exposure; alcohol, number of drinks per week multiplied by number of years; smoking, number of years; intoxication, refers to the history of episodes of accidental episodes of poisoning with solvents. The value represents number of persons; RNE, recreational noise exposure in years; tenure, years working at the factory.

TABLE 2
Gmean, GSD, and Range of Airborne Concentrations for MEK and Toluene for Group 2 and Group 3 Workers

	Group 2		Group 3	
Solvent	Gmean (GSD)	Range	Gmean (GSD)	Range
MEK (n = 111)	5.81 (3.82)	0.3–64	12.45 (2.34)	1.00–104
Toluene (n = 110)	3.21 (3.17)	0.3–26	4.77 (4.18)	0.001–131

Values are in parts per million.

n indicates number of samples; Gmean, geometric mean; GSD, geometric standard deviation; MEK, methyl ethyl ketone.

Audiological Evaluation

Otoscopy was carried out on all subjects to check the absence of obstructive cerumen and the eardrum aspect. Middle ear function was checked by immittance audiometry using a GSI37 middle ear analyzer.

Air conduction pure-tone thresholds (PTA) from 0.5 to 8 kHz and high frequency PTA at 12 and 16 kHz were obtained using an Interacoustics AC40 clinical audiometer (Assens, Denmark). Pure-tone audiometry is a participative test used to determine hearing sensitivity. Pure-tone thresholds indicate the lowest sound audible to an individual at least 50% of the time. TDH-39P headphones (Assens, Denmark) were used for conventional pure-tone audiometry (0.5–8 kHz) and Koss R/80 headphones for high-frequency pure-tone audiometry. Both pure-tone audiometries (including high frequency) and the DD test were conducted in a double-walled, sound-treated booth that met American National Standards Institute standards for hearing test environments.[30]

The DD test[29] was carried out to assess central auditory functioning, specifically dichotic listening. This test involves central auditory structures that allow subject's ability for dichotic listening. Twenty sets of two pairs of digits in English, digitally recorded in a compact disc, were presented dichotically (at the same time to both ears) at 50 dB above the average threshold for the frequencies 0.5, 1, and 2 kHz. The test required the use of a compact disc player connected to the audiometer specified above. A 1000-Hz calibration tone recorded in the compact disc was used to determine output intensity. The output intensity was controlled from the audiometer. Subjects were asked to repeat each set of four numbers. The repetition task involved free recall. A total percentage score was obtained by counting the correctly repeated numbers.

Descriptive Analysis

Audiograms from conventional pure-tone audiometry (0.5–8 kHz) were classified by a trained audiologist as normal or abnormal. Abnormal audiogram was defined as the one with the presence of at least one single hearing threshold equal or worse than 30-dB HL. Abnormal audiograms were classified as high-frequency HL (including a single notch for high frequencies) or other shapes such as flat audiograms or a notch for a nonhigh frequency hearing threshold. Hearing impairment was also calculated according to the model proposed by the American Academy of Otolaryngology-79 and the American Medical Association. These professional associations define hearing impairment as an average for the hearing thresholds at 0.5, 1, 2, and, 3 kHz equal or worse than 26 dB. Using this definition, a total of subjects with hearing impairment was calculated.

For the purpose of analysis, the following outcome measures of hearing were examined: binaural average of PTA for both ears at 3, 4, and 6 kHz, binaural average of high-frequency audiometric thresholds (HFA) at 12 and 16 kHz, and binaural average of DD scores. Binaural average of PTA is expressed by the following equation: [(right ear threshold at 3 + 4 + 6 kHz) + (left ear threshold at 3 + 4 + 6 kHz)]/6. Binaural average of HFA is expressed by the following equation: [(right ear threshold at 12 + 16 kHz) + (left ear threshold at 12 + 16 kHz)]/4. Binaural average of DD scores is expressed by the following equation: (right ear scores + left ear scores)/2.

Statistical Analysis

To focus on risk factors for sensorineural HL, only the workers with normal middle ear were included in the analysis.

The outcome measures of hearing were compared between solvent exposure groups using Fisher least significant difference (LSD) test. Also, a second analysis was performed (using Fisher LSD test) to compare DD test score and HFA thresholds across groups only including normal-hearing subjects. This was to explore the effect of HL on these two hearing outcomes. The 95% confidence level ($\alpha = 0.05$) was used in all tests of significance. Simple linear regression analyses were carried out to examine associations between hearing outcomes and the continuous covariates of age, smoking (number of years), alcohol consumption (number of years multiplied by number of drinks per week), number of years working at the factory, and years of recreational noise exposure. All factors were considered to be continuous variables. In addition, the categorical variables of gender, race, ethnicity (Hispanic vs non-Hispanic), solvent exposure group, and acute intoxication with solvents (Y/N) were compared with hearing outcomes using simple linear regression.

Multiple linear regressions were then performed to separately model the association between each of the three outcome measures of hearing and the risk factors for HL tested in the simple linear regression models. A backward elimination technique was used with each model to select those risk factors remaining significant in the adjusted analysis, using a selection criterion of $\alpha < 0.05$. To investigate possible confounding effects of particular covariates, the models included interaction terms between solvent exposure group and years at the factory, solvent exposure group and ethnicity (Hispanic), solvent exposure group and gender (male), and age and gender (male). In addition, for the DD outcome, we performed a stratified analysis including only the Hispanic population ($n = 71$), and we tested for the stability of the model. This was to investigate for a possible effect of language (Spanish) on the DD test results (dichotic presentation of numbers in English). All statistical analyses were performed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC).

Results

Pure-Tone Thresholds

Figure 1 shows the mean for hearing thresholds across the assessed frequencies (0.5–16 kHz) and mean comparisons among groups for the left ear.

From the selected 110 participants, 41 subjects had normal audiograms, and 69 subjects abnormal audiograms (5 [25%] subjects from group 1, 11 [61%] from group 2, and 53 [73.6%] from group 3). From the 69 subjects with abnormal audiogram, 7 subjects had unilateral HL (all of them from group 3), and 62 bilateral HL (5 subjects from group 1, 11 subjects from group 2, and 46 subjects from group

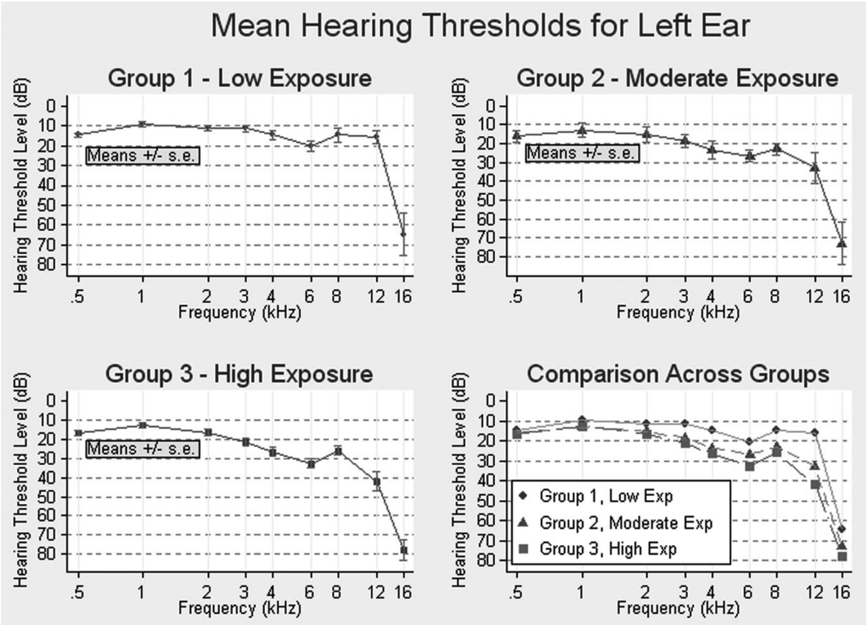

Fig. 1. Using the Fisher LSD test, there were no significant differences between groups 1 and 2 for all the frequencies. Significant differences between groups 1 and 3 at 3 kHz ($P = 0.022$), 4 kHz ($P = 0.016$), 6 kHz ($P = 0.011$), 8 kHz ($P = 0.024$), and 12 kHz ($P = 0.007$). No significant differences between groups 2 and 3 for all the frequencies.

TABLE 3
Hearing Scores for the Three Subgroups of Workers

	Group 1 (n = 20)				Group 2 (n = 18)				Group 3 (n = 72)			
Outcome	Mean	SD	Median	Range	Mean	SD	Median	Range	Mean	SD	Median	Range
PTA	13.8	8.9	10.0	3.3 to 38.3	23.1	17.0	17.5	5 to 65.8	25.5	16.6	20	2.5 to 71.7
HFA	39.1	28.9	40.6	−3.8 to 77.5	54.9	36.1	61.3	3.8 to 110	59.1	38.6	61.3	−7.5 to 110
DD	86.5	9.9	87.3	63.5 to 100	66.1	17.7	60.8	38.5 to 100	61.5	21.3	57.5	0 to 100

Group 1 includes workers with the lowest solvent exposure; group 2, workers with moderate solvent exposure; group 3, workers with the greatest solvent exposure.

PTA indicates pure-tone audiometry thresholds (3–6 kHz) in dB; HFA, high-frequency audiometry thresholds (12–16 kHz) in dB; DD, dichotic digits in percentage of corrected repeated items; SD, standard deviation.

3); 60 subjects showed high-frequency HL (including a single notch for high frequencies), and 9 showed other shapes such as flat audiograms or a notch for a nonhigh-frequency hearing threshold. In terms of hearing impairment (American Academy of Otolaryngology-79), a total of 22 subjects showed the presence of hearing impairment (3 subjects from group 2 [16.6%] and 19 subjects from group 3 [26.4%]).

Hearing Comparison Between Groups

Differences among groups for age and the three hearing outcomes were explored using one-way analysis of variance with the post hoc Fisher LSD test. Significant differences among groups were found for PTA (F = 4.44), HFA (F = 2.31), and DD (F = 13.33). PTA and HFA thresholds were statistically better (lower) for group 1 workers than group 3 workers (mean difference: −11.67, P = 0.004; mean difference: −19.94, P = 0.034). For DD, group 1 workers obtained statistically better (higher) results than group 2 workers (mean difference: 20.39, P = 0.001) and group 3 workers (mean difference: 25.07, P = 0.000). Table 3 shows descriptive statistics for the three studied outcomes.

The stratified analysis including only normal-hearing subjects for DD and HFA showed for one-way analysis of variance significant differences among groups for DD (F = 9.004, P = 0.001) only. DD results were better (higher) for group 1 workers, intermediate for group 2 workers, and worse for group 3 workers (mean difference: group 1 vs group 2, P = 0.259; group 1 vs group 3, P = 0.000; group 2 vs group 3, P = 0.044).

TABLE 4
Simple and Multiple Linear Regression Analysis for PTA Outcome

	Bivariate Model		Multivariate		Final Multivariate	
Characteristics	β	P	β	P	β	P
Age	0.631	0.000	−0.108	0.770	−0.045	0.845
Male	0.297	0.002	1.032	0.024	−0.759	0.007
Caucasian	0.147	0.134	0.166	0.112		
Hispanic	0.161	0.095	0.138	0.580		
Solvent exp.						
HE	0.218	0.022	0.532	0.075	0.285	0.011
ME	0.003	0.971	−0.037	0.919	0.126	0.221
LE (reference)						
Tenure	0.300	0.001	0.253	0.397		
Risk factors						
Cigarettes	0.102	0.291	−0.104	0.230		
Alcohol	0.184	0.055	0.134	0.146		
RNE	0.210	0.029	0.166	0.049		
Intox	−0.041	0.671	−0.062	0.409		
Interactions						
Hisp × HE			−0.236	0.424		
Hisp × ME			0.076	0.691		
HE × tenure			−0.243	0.407		
ME × tenure			−0.388	0.063		
Male × HE			0.339	0.278		
Male × ME			0.645	0.075		
Male × age			1.219	0.037	1.160	0.003

Solvent exp indicates solvent exposure group; HE, high exposure; ME, moderate exposure; LE, low exposure; tenure, number of years working at the factory; cigarettes, total number of smoking years; alcohol, number of drinks per week multiplied by number of years; RNE, number of years recreationally exposed to noise; Intox, acute intoxication with solvents; Hisp, Hispanic.

Multiple Regression Analysis

Using multiple linear regression analysis for each outcome independently, the mean air conduction hearing threshold (PTA, 3–6 kHz), the mean air conduction hearing thresholds for high frequency (HFA, 12 and 16 kHz), and mean score for DD were not significantly predicted by smoking, alcohol consumption, years working at the factory, recreational noise exposure and acute intoxication with solvents (Tables 4–6). As Table 4 shows, variables remaining significantly associated with PTA in the final multiple linear regression model included gender (male) and solvent exposure group. Also, a significant association between PTA outcome and the interaction term be-

TABLE 5
Simple and Multiple Linear Regression Analysis for HFA Outcome

	Bivariate Model		Multivariate		Final Multivariate	
Characteristics	**β**	***P***	**β**	***P***	**β**	***P***
Age	0.661	0.000	0.778	0.035	0.661	0.000
Male	0.301	0.001	0.224	0.612		0.995
White	0.193	0.048	0.332	0.002	0.193	0.009
Hispanic	0.062	0.520	0.012	0.962		
Solvent exp.						
HE	0.161	0.093	0.155	0.593	0.253	0.009
ME	0.001	0.989	−0.122	0.730	0.176	0.075
LE (reference)						
Tenure	0.358	0.000	−0.108	0.713		
Risk factors						
Cigarettes	0.175	0.068	0.033	0.696		
Alcohol	0.077	0.429	−0.057	0.528		
RNE	0.100	0.299	−0.017	0.832		
Intox	0.054	0.577	0.060	0.411		
Interactions						
Hisp × HE			−0.259	0.372		
Hisp × ME			0.064	0.734		
HE × tenure			0.177	0.539		
ME × tenure			−0.205	0.314		
Male × HE			0.124	0.684		
Male × ME			0.387	0.274		
Male × age			−0.227	0.688		

Solvent exp indicates solvent exposure group; HE, high exposure; ME, moderate exposure; LE, low exposure; tenure, number of years working at the factory; cigarettes, total number of smoking years; alcohol, number of drinks per week multiplied by number of years; RNE, number of years recreationally exposed to noise; Intox, acute intoxication with solvents; Hisp, Hispanic.

TABLE 6
Simple and Multiple Linear Regression Analysis for the DD Outcome

	Bivariate Model		Multivariate		Final Multivariate	
Characteristics	**β**	***P***	**β**	***P***	**β**	***P***
Age	−0.167	0.084	−0.057	0.906	−0.172	0.047
Male	−0.286	0.003	0.242	0.679		
White	−0.073	0.459	0.097	0.474		
Hispanic	−0.380	0.000	0.006	0.985	−0.260	0.009
Solvent exp.						
HE	−0.347	0.000	−0.131	0.734	−0.386	0.002
ME	−0.015	0.881	0.299	0.521	−0.274	0.015
LE (reference)						
Tenure	0.014	0.883	0.184	0.635		
Risk factors						
Cigarettes	−0.044	0.649	−0.093	0.409		
Alcohol	−0.042	0.670	−0.075	0.531		
RNE	0.072	0.459	0.026	0.811		
Intox	−0.018	0.856	−0.005	0.956		
Interactions						
Hisp × HE			−0.439	0.251		
Hisp × ME			−0.263	0.293		
HE × tenure			−0.109	0.774		
ME × tenure			−0.059	0.826		
Male × HE			−0.102	0.800		
Male × ME			−0.489	0.295		
Male × age			−0.215	0.774		

Solvent exp indicates solvent exposure group; HE, high exposure; ME, moderate exposure; LE, low exposure; tenure, number of years working at the factory; cigarettes, total number of smoking years; alcohol, number of drinks per week multiplied by number of years; RNE, number of years recreationally exposed to noise; Intox, acute intoxication with solvents; Hisp, Hispanic.

tween age and gender (male) was observed. HFA thresholds (Table 5) were best predicted by age, race (white), and solvent exposure group. The mean score for DD (Table 6) was best predicted by age, ethnicity (Hispanic), and solvent exposure group. The stratified analysis (including only normal-hearing subjects, data not shown) for DD showed similar estimates for solvent exposure group. The new estimates (β) were −0.471 for group 3 (highest exposure) and −0.382 for group 2 workers (moderate exposure) in comparison with −0.386, and −0.274, respectively, from the model including all the subjects.

Discussion

The results of this study confirm that occupational exposure to organic solvent mixtures has an adverse effect 1) on standard PTA (3–6 kHz), 2) on HFA (12–16 kHz), and (3) on central auditory function.

The demographic profile of the workers in the three solvent groups differed by ethnicity, race, and socioeconomic status. Most of group 3 workers were Hispanic whereas most of group 1 subjects were non-Hispanic. Subjects in the lower solvent group from group 1 were more likely to have administrative jobs that may be associated with higher socioeconomic status compared with factory production jobs. Therefore, it is possible that the observed effect of solvents on hearing status was due at least in part, to some confounding by race and socioeconomic factors.[31,32] For this reason, we modeled hearing outcome as a function of variables previously known to affect hearing such as race, gender, and age.[33–35] We then investigated if adding our predictors significantly increased the fit of the model. The effect of solvents remained significant after taking into account these factors. Therefore, although we cannot eliminate the possibility of residual confounding, we believe that the observed relationship between hearing status and solvents may be related to ototoxic effects of solvent exposures.

As previously reported,[17,18] our findings suggest that solvents, even in the absence of excessive noise exposure, have a deleterious effect on PTA between 3 and 6 kHz. Previous investigations have studied populations of workers simultaneously exposed to solvents and excessive noise. The present research confirms that workers not exposed to excessive noise may still be at risk for work-related HL when agents such as solvents are present in their workplace.

HFA (12–16 kHz) were observed to be significantly increased (worse) among group 3 workers in comparison to group 1 workers. Similar results were found by Muijser et al,[36] who described HFA thresholds significantly increased in those workers with the greatest exposure to styrene in comparison with those workers less exposed.

Significant differences between groups for HFA were not found when only normal-hearing subjects (in the 0.5– 8 kHz audiometric range) were compared. We compared normal-hearing subjects between groups to investigate whether HFA may be a useful early indicator of SIHL. When subjects with normal hearing thresholds between 0.5 and 8 kHz show abnormal HFA thresholds, then an auditory dysfunction is suspected. HFA has been suggested as a tool for the early identification of cochlear pathology in oncologic patients under treatment with ototoxic drugs[37] and in patients with chronic renal failure.[38] The use of HFA for the early identification of noise-induced HL has also been studied.[39,40] If a person has acquired a cochlear HL, HFA thresholds will be affected. This is probably the reason why significant differences between groups were found when all workers were compared, regardless of their hearing level. Group 3 workers had the highest percentage of HL, and this group indeed seemed to have the worst HFA thresholds.

Based on the findings from this study, it is difficult to conclude that this assessment tool can be a pertinent early indicator of cochlear dysfunction induced by solvent exposure. It should be noted that, first, the mean for HFA thresholds for normal-hearing subjects was still higher (worse) for group 3 workers and lower (better) for group 1 workers. Therefore, it is possible that the fact that the difference was not statistically significant was related to the relatively small sample size. Second, the cross-sectional design of the study may have accounted for this result. Previous research demonstrating the utility of HFA has compared intrasubject changes/differences for HFA thresholds (ie, pre- and post-drug treatment, pre- and postnoise exposure). HFA thresholds seem to be different for person to person even if they have normal-hearing thresholds. Thus, to study the utility of HFA to early identify SIHL, intrasubject differences rather than intersubject differences should be studied. Because of logistic limitations, this was not possible in this study. Future longitudinal studies in solvent-exposed populations monitoring intrasubject changes for HFA (with no changes in PTA thresholds) should be conducted to clarify the utility of this procedure to early identify SIHL. We conclude that currently, HFA cannot be considered as a pertinent early indicator for SIHL.

Previous animal and human studies have suggested that due to their neurotoxic effects, solvents may induce central auditory dysfunction. In our study, workers of group 3 obtained the lowest score for DD, a central auditory processing test, in comparison with those of groups 1 to 2. The multiple linear regression showed a significant correlation between solvent exposure and DD scores. Similar as we did for HFA, a further analysis incorporating only workers with normal-hearing thresholds was performed. Differences for DD among groups were still observed. Group 3 workers showed significantly worse DD results than group 1 workers and group 2 workers, even when all the workers compared did not have HL. Therefore, these results suggest an association between solvent exposure and dichotic listening performance (central auditory function) as measured by the DD test. This finding implies that the DD may be a useful tool to detect central auditory dysfunction induced by solvent exposure. Furthermore, because of the ease of administration of this test, the DD test can be an adequate option to monitor the central auditory function of solvent-exposed workers.

From the results of this study is not possible to conclude whether the decrement in hearing thresholds and the central auditory dysfunction is part of a continuum or if both signs are triggered by two different mechanisms. Recently, toluene was shown to act on the auditory efferent system and thereby inhibit the acoustic protective reflexes in the rat.[15] Occupational exposures to toluene were associated with increased acoustic reflex decay.[2] Findings of this study lead to a hypothesis that solvents induce a subtle central auditory dysfunction at early stages, as observed by dichotic listening. Then the adverse effects of solvents progress to the periphery of the auditory system (the cochlea) triggering poor hearing thresholds. This may explain why dichotic listening was significantly worse among group 3 workers with normal hearing thresholds in comparison with group 1 workers. For group 3 workers, solvents have induced auditory impairment that has not progressed to the cochlea yet. Two independent mechanisms may be related to SIHL. One mechanism may only induce cochlear dysfunction whereas the other one only induce central auditory dysfunction. Thus, both mechanisms and variables such as subject's susceptibility may account for differences in which mechanism is more prominent. This may explain why some group 3 workers had normal hearing thresholds but abnormal DD results, and some of them poor hearing thresholds and abnormal DD scores. For those subjects with normal hearing thresholds but abnormal DD scores, the mechanism related to central auditory dysfunction was predominant. For those subjects with poor hearing thresholds and abnormal DD scores, both mechanisms were equally predominant. Barregård and Axelsson[41] suggested that the auditory effects of solvents are due to a combination of ototoxicity and neurotoxicity. This claim supports the hypothesis that SIHL is generated by two different and independent mechanisms. The ototoxicity is thus the mechanism that impairs the cochlea, specifically the outer hair cells as shown in animal models. The observed outcome is poor hearing thresholds at the mid- and high-frequency range. The neurotoxicity on the other hand, is the mechanism that induces impairment on the central auditory pathways. Signs such as abnormal dichotic listening performance, as observed in the present research, or other previously reported signs[21,22] such as speech discrimination and sound localization difficulties may be part of the adverse auditory outcomes of this mechanism.

Our finding that age and gender were associated with HL risk as measured by PTA was consistent with multiple other studies. It has been previously reported that male workers have worse hearing than female workers.[33] For the DD outcome, not only age and solvent exposure group were significantly associated with DD results but also ethnicity (Hispanic) seemed to be significantly associated with this outcome. The DD test is an auditory processing test that uses numbers in English as stimuli. Hispanics can use predominantly Spanish as a medium of oral communication. English is used when they communicate with non-Hispanic coworkers. Thus, part of the observed effect of solvents on DD may be due to linguistic differences among the groups, as group 3 workers were predominantly Hispanics. For future studies, the use of DD test in the participants' native language, if available, is recommended. However, as mentioned earlier, we examined interaction effects and still found an effect of solvents on DD. In addition, we performed a stratified analysis including only the Hispanic population ($n = 71$), and we tested for the stability of the model. The new regression analysis, when only Hispanics were included, showed similar estimates for solvent exposure group. The stability of the estimates in the stratified analysis confirms the fact that solvents may induce central auditory dysfunction.

One of the limitations of this study was the lack of detailed information on personal solvent and noise exposure. This may have resulted in exposure misclassification. However, because such misclassification is likely to be nondifferential, especially because the industrial hygienist was unaware of the hearing status of the study individuals, it would tend to bias results toward the null and not explain our findings of a relationship between solvent exposure and hearing. Future studies should include more detailed solvent exposure assessments. Animal studies have demonstrated that the solvent concentrations required to induce auditory damage in experimental animals are usually much higher than the concentrations observed in the industry. However, different studies have demonstrated that much lower levels observed in industry were sufficiently high to be associated with hearing deficits.[19,42,43] It has been suggested that auditory effects of solvents have been observed at lower concentrations in humans because human subjects are generally exposed to solvents in combination with a pool of other factors (several exposures, physical demands, etc) whereas animal experiments typically involve isolated solvent exposures. Evidence on this issue comes from a study[44] that demonstrated that solvents concentrations required to induce auditory damage are much lower for active rats in comparison with sedentary rats.

The effects of environmental/occupational chemicals are not restricted to the cochlea. Reports have indicated that retrocochlear and central effects can also be linked to these exposures.[20–22] Results of this study also show that solvents may induce central auditory dysfunction as observed by abnormal dichotic listening. Morata et al[2] suggested that professionals who perform hearing tests should take notice when workers complain of hearing difficulties that are not reflected in the audiometric results and should consider a referral for further testing. Evidence from this and other studies has demonstrated that pure-tone audiometry is not enough to assess SIHL. A conference on the deleterious effects of noise and solvents on the auditory system was held in Lodz, Poland.[45] Among the suggestions arisen from this conference, the need to include central auditory tests in the monitoring of SIHL was highlighted. This study provides evidence that the DD test is a sensible clinical tool for the detection of central auditory dysfunction associated with solvent exposure. The DD test is easy to administer, requires ~8 minutes to be completed and is currently available in different languages.[46–49] All these features make the DD an appropriate tool to be used when monitoring the hearing of solvent-exposed workers.

According to our results, we suggest the inclusion of solvent-exposed workers in HL prevention programs. We conclude that solvent-exposed workers' hearing should be monitored using both peripheral and central auditory tests. For the assessment of central auditory function, we suggest the utilization of the DD due to its sensibility and ease of administration.

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