CME Article #1

Audiometric Findings in Workers Exposed to Low Levels of Styrene and Noise

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Learning Objectives

- Explain whether and how exposure of workers to styrene in the course of making fiberglass products, and to high noise levels, interact to produce bilateral high-frequency hearing loss.
- Recall the personal and environmental factors that were significantly associated with hearing loss in this study.
- Discuss how these findings relate to past studies in animals and styrene-exposed workers, and take note of relevant public health considerations.

Abstract

Audiometry and exposure measurements were conducted on workers from fiberglass and metal products manufacturing plants and a mail distribution terminal (N = 313). Workers exposed to noise and styrene had significantly worse pure-tone thresholds at 2, 3, 4, and 6 kHz when compared with noise-exposed or nonexposed workers. Age, noise exposure, and urinary mandelic acid (a biologic marker for styrene) were the variables that met the significance level criterion in the multiple logistic regression. The odds ratios for hearing loss were 1.19 for each increment of 1 year of age (95% confidence interval [CI], 1.11–1.28), 1.18 for every decibel >85 dB(A) of noise exposure (95% CI, 1.01–1.34), and 2.44 for each millimole of mandelic acid per gram of creatinine in urine (95% CI, 1.01–5.89). Our findings suggest that exposure to styrene even below recommended values had a toxic effect on the auditory system. (J Occup Environ Med. *2002;44:806–814*)

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Mention of any company or product name(s) is for identification only and does not constitute endorsement by NIOSH.

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Workers from several economic sectors are commonly exposed to combinations of chemical or physical agents, but knowledge about the potential health effects of these combinations is limited.[1] Reports on the auditory effects of chemicals—such as solvents, metals, and asphyxiants—on hearing and their interaction with noise illustrate physical-chemical interactions. This interaction has been studied more systematically in the last decade. The importance of this area is underscored by the dearth of publications on the risk of developing hearing loss from occupational factors other than noise and by the ubiquitous use of chemical agents.[2,3]

When most international noise standards were originally promulgated, there was little evidence of hearing losses induced by industrial chemicals or their interactions with noise. However, it is clear today that noisy industrial settings can often have other potentially dangerous factors for hearing.[4,5]

Styrene Effects on the Auditory System

Animal experiments have shed light on the ototoxicity of styrene.[6–10] (For a recent review, see Morata and Campo.[11]) Styrene exposure can cause permanent and progressive damage to the auditory system in rats even after exposure has ended.[12] Styrene has been shown to be a more potent ototoxicant than toluene, and it can have a synergistic effect when presented together with noise or ethanol.[13,14]

Earlier field studies that assessed styrene effects on auditory function

identified only minimal effects of the chemical on pure-tone thresholds.[15–17] More recently, two studies investigated the effects of styrene exposure in male workers in factories that produced plastic buttons or bathtubs.[18,19] A study was conducted of workers with noise exposures <85 dB(A) and exposures to low concentrations of mixtures of chemicals containing mostly styrene and toluene.[18] A subsequent study divided 48 participants into three subgroups by their exposure condition: an unexposed group, a group exposed to low levels of styrene (2.9–28.9 ppm) and noise [69–76 dB(A)], and a group exposed to noise levels that ranged from 82 to 86 dB(A). Although both noise levels and styrene concentrations in the air were within limits recommended by several international agencies, the high-frequency hearing thresholds were poorer in workers exposed for >5 years. This effect was associated with styrene concentrations in air and mandelic acid concentrations in urine.[18,19]

As part of a large investigation conducted in Poland ($N = 1366$), the auditory effects of several solvents and noise were studied in a group of styrene-exposed workers (M. Sliwińska-Kowalska et al, unpublished observations) and compared with a group of unexposed workers and another group exposed to noise and other solvents.[20] Exposure assessment included data from interviews, company records, and site measurements of noise intensities for different work tasks. The participants from the styrene group were exposed to noise intensities ranging from 78 to 86 dB(A). Average styrene exposures (8-hour values) ranged from 11 to 38 ppm and had a maximum level of 120 ppm. Hearing loss (>25 dB at more than one frequency >2 kHz) was observed in 70% of the workers exposed to styrene and noise compared with 16% of the unexposed workers. The prevalence of hearing loss among groups that experienced exposures to other solvents in paint and lacquer or to exposures in the furniture manufacturing industries ranged from 56% to 67%, whereas for the noise-exposed group, it was 20%. Significantly higher mean audiometric thresholds ($P < 0.05$) were observed in the styrene-exposed workers at 2, 4, and 6 kHz when compared with the noise-only and the unexposed groups. When compared with the other solvent-exposed groups, mean thresholds for the styrene-exposed group were also significantly higher at the frequencies of 4 and 8 kHz. The risk for developing a hearing loss was 12 times greater (95% confidence interval [CI], 5.7–19.2) for styrene-exposed workers compared with the unexposed group.

The aim of the present study was to investigate the effects of occupational exposure to low levels of styrene and noise on the auditory system.

Methods

The selection of styrene and the fiberglass products (FGP) industry took into consideration styrene's potential neurotoxicity, available evidence of ototoxicity, severity of the problem, accessibility and reliability of industry exposure records, accessibility to workers, and magnitude of an occupationally exposed population. Although exclusive chemical exposure to solvents is rare, the FGP industry is one of the few occupational settings that has an almost monoexposure to styrene (small amounts of acetone are used for cleaning tools in FGP industries). Eleven FGP manufacturers varying in size from five to 500 employees agreed to participate in this study. From those, 154 styrene-exposed workers participated, of whom 65 who were not exposed to excessive noise levels [>85 dB(A) time-weighted-average [TWA]]. Noise-exposed subjects ($n = 78$) were selected from three companies in the metal products manufacturing industry, and the nonexposed subjects ($n = 81$) were selected from a mail distribution terminal.

All styrene-exposed workers employed for a minimum of 1 year in the FGP companies were invited to participate in the study. The workers from the metal industry were selected on the basis of noise exposure levels that were equivalent to those of the FGP workers. The unexposed controls were randomly chosen from a large number of employees in a mail distribution terminal. The noise levels in the terminal were <85 dB(A) TWA. The project was approved by the Karolinska Institute Ethics Committee, as required by the Swedish Foundation for Work Life Research.

Dropouts

Originally, 329 workers met the eligibility criteria and were invited to participate in the study, but 10 styrene-exposed workers did not participate, 3 because of illness at the time the hearing measurements were taken and 7 for other undisclosed reasons. Of the remaining 319 workers who participated in the audiometric tests, 3 were excluded from the analyses because of their incapability to perform the tests and 3 more because of missing questionnaires, which caused a lack of background and exposure data. Thus, a total of 313 subjects, 278 men and 35 women (11%), were included in the study.

Data were collected through a questionnaire on work history, medical history, occupational and nonoccupational exposures, and lifestyle factors. The self-reported medical history included data on diabetes, prior ear surgery, head injury, high fever, measles, high blood pressure, mumps, ear infections, history of hearing loss in the family, ototoxic medication use, and tinnitus. The questionnaires were mailed to participants 1–2 weeks before the testing began. The participants were instructed to return the questionnaire at the time of the test. On the day of testing, interviewers examined the questionnaire with each subject to

check for invalid answers or unanswered questions.

Styrene Exposure Assessment

To determine the level of exposure to styrene, TWA exposure evaluations were conducted on all subjects exposed to styrene and in five of each of the other groups for control purposes only. Air from the breathing zone of each subject was collected by passive samplers (automated thermal desorption [ATD] tubes) filled with 0.20 g of Tenax (TA 60–80 mesh, Chrompack No. 2440). Two successive samples were collected for each worker, and the average collection time was 3 hours, 50 minutes. After exposure monitoring was completed, the ADT samples were securely sealed with brass caps, stored in a freezer, and sent to the National Institute for Working Life in Stockholm, Sweden, for gas chromatography (GC) analysis.

Analysis of Personal Air Samples

Samples were desorbed (Perkin-Elmer system ATD-400) and analyzed by GC (Perkin-Elmer Auto system). The thermal desorption was set at the following parameters: desorption oven 250°C, desorption time 5 minutes, valve 200°C, trap −30°C, high 300°C with a 3.0-minute hold, line 200°C. The pressure was 3 psi, the desorption flow was 55.6 mL/minute, and the outlet split was 9.8 mL/minute. In the GC analysis, a Chrompack capillary column (CP-Sil 8CB, 25 m, internal diameter 0.32 mm, coating 2 μg) was used. Nitrogen was used as the carrier gas at a column pressure of 4.5 psi. The injector and detector temperatures were 200°C and 250°C, respectively. The column was kept isothermal at 80°C for 5 minutes, then heated by 5°C/minute to 150°C, further heated by 25°C/minute to 250°C, and finally kept isothermal for 10 minutes. Standard curves in the appropriate concentration interval were prepared by diluting styrene in methanol and injecting them in ATD tubes. The relative standard deviation was estimated to be 1.5%.

The historical styrene exposure assessment was based on a calculated mean value, taken from the records of the mandatory annual styrene exposure measurements made by each company, over at least a 10-year span. For each subject, the total lifetime cumulative styrene exposure (CSE) was calculated according to the following formula:

$$CSE = \sum_{i=1}^{n} (t_i * \exp_i)$$

where n = the number of jobs, t_i = time in years at each job, and exp_i = exposure to styrene in milligrams per cubic meter (mg/m^3) for each job.

Total styrene exposure was assessed by the biological monitoring of mandelic acid and creatinine in the urine of 127 styrene-exposed workers. These workers collected their urine during a 24-hour period. Collection started at the beginning of their work shift. Air measurements were collected during the same day. After measurements of the total urine volume were completed, two additional 10-mL samples of urine were taken for analyses by high-pressure liquid chromatography (HPLC) at the National Institute for Working Life, Stockholm, Sweden.

Analysis of Mandelic Acid and Creatinine in Urine

Mandelic acid and creatinine in urine were analyzed by HPLC. Standard solutions were prepared ranging in concentration from 0.25 to 4.0 mg/mL. Urine samples were diluted 100-fold with distilled water. The diluted samples were centrifuged at 2000 rpm × 5 minutes, and 10 μl of the supernatant thus obtained was used for HPLC. The HPLC instrument (Hewlett-Packard 1050) was equipped with an autosampler, an octadecyl silane column (Hichrom, Chrompack, 4.6 mm × 150 mm), a diode-array detector, and an integrator (HP Chemstation v. 5.02). *Ortho*-methylhippuric acid (1 mg/mL) was used as the internal standard. Peak identification was made by comparison of retention times and ultraviolet-visible spectra (190–600 nm) against spiked samples. Quantification was determined by isolating the peak area at 210 nm. The detection limit corresponded to 0.1 mmol/L and 0.004 mmol/L for mandelic acid and creatinine, respectively. The levels of mandelic acid were normalized to creatinine levels before the statistical analyses and reporting.

Noise Exposure Assessment

Noise exposure was assessed by personal exposure measurements performed with noise dosimeters (Brüel & Kjær 4436). The dosimeters stored the maximal sound level every second (fast time weighting, 3-dB exchange rate). The microphone was mounted pointing upward on the worker's right lapel. The time of collection varied between 2.5 and 12 hours (mean of 7.6 hours). Background noise levels were measured during a walk-through survey by using a direct-reading Brüel & Kjær 2218 sound-level meter with a ½-inch Brüel & Kjær 4165 microphone mounted on an extension rod. All instruments were calibrated before measurements were taken.

Exposure assessments were calculated individually, based on 8-hour level-equivalent dosimeter measurements, L_{eq8} dB(A). At least one full-shift noise dosimetry was performed for all different work tasks. Workers whose personal noise dosimetry was not performed (n = 128) were assigned a mean value of the noise levels obtained from workers performing the same work tasks. Estimates of exposure during work at jobs held before the present one were calculated, based on information given by the worker, eg, if the workplace was "quiet" or "very noisy." Information on typical noise levels in certain industries was found in the literature (NoiseScan database[21])

TABLE 1
Characterization of the Study Population ($N = 313$)

Variable	Nonexposed ($n = 81$)	Noise Exposure ($n = 78$)	Styrene Exposure ($n = 65$)	Styrene and Exposure Noise ($n = 89$)
Age (yrs)	45 (26–62)	42 (20–64)	43 (21–62)	43 (21–65)
Tenure* (yr)	18 (2–38)	12 (1–35)	17 (1–39)	15 (2–37)
Previous noise exposure [≥85 dB(A) TWA; yr)]	7 (0–25)	12 (1–26)	5 (0–16)	6 (0–21)
Exposures				
Current noise level [dB(A)]	77 (69–86)	85 (75–116)	82 (75–84)	89 (85–108)
Lifetime noise exposure [dB(A)]	79	86	84	89
Current styrene exposure (mg/m^3)	· · ·	· · ·	16 (0.2–96)	12 (0.03–50)
Mandelic acid in urine (mmol/g creatinine)	· · ·	· · ·	0.9 (<MDC–2.9)	0.9 (<MDC–3.0)
Lifetime styrene exposure (mg-yr/m^3)	· · ·	22.4	1303	884

Mean values and range (within parentheses) for the variables of age, tenure, previous noise exposure, current noise and styrene exposures, and estimated lifetime noise and styrene exposures.

* Indicate variables that met the significance level criterion ($P < 0.0001$) for differences between groups. MDC, Minimum detectable concentration.

and included in the estimation of past exposure. For each subject, the total cumulative noise exposure (CNE) was calculated according to the following formula:

$$CNE = 10*\log\sum_{i=1}^{n}(10^{((L_{eq8i}/10)+\log(T_i/T_n))})$$

Where n = the number of jobs, L_{eq8i} = the equivalent continuous sound for 8 hours, in dB(A), T_i = the exposure duration associated with L_{eq8i}, in years, and T_n = the total exposure duration in years (sum of time in all jobs when the subject was exposed to noise).

The characteristics of the study population regarding their age, tenure, and current and previous exposures to the studied agents are presented in Table 1.

Testing the Auditory System

A bus was converted into a mobile laboratory and equipped with two soundproof booths that met the requirements of ISO 8253-1 for audiometric testing environments. Otoscopy was performed to screen for conditions that would exclude a person from the study, ie, external otitis or perforated tympanic membrane.

Equipment

For pure-tone audiometry, a technical audiological measurement processor (TAMP3, Unit of Technical Audiology, Karolinska Institute) was used. TAMP3 is based on the signal processor Texas Instruments TMS32010 and was controlled by a personal computer. It was equipped with a 96-kb memory, alternating- and direct-current converters, a real-time clock, anti-aliasing filters, controllable attenuators, amplifiers with a controllable gain, and an output amplifier suited for driving the headphone type TDH-39 with an MX-41AR cushion. Acoustic calibration of the equipment according to ISO 389 was performed after each installation of the equipment in the bus (twice) and after each measurement period as a check (twice).

Pure-Tone Audiometry

Pure-tone thresholds were measured with the fixed-frequency Békésy method for both ears at the frequencies 1, 2, 3, 4, 6, and 8 kHz. Daily biological calibration checks were also performed immediately before the subjects were tested.

Data Analysis

Each audiogram was evaluated for hearing loss. The audiogram was considered normal if thresholds did not exceed a 25-dB hearing level at any tested frequency. If the audiogram revealed a "notch" at one of the frequencies between 3 and 6 kHz (as in noise-induced hearing-loss cases) or if the thresholds were poorest in this frequency range, the audiogram was classified as high-frequency hearing loss. A nonoccupational category was included to account for those hearing losses that could not be attributed to occupational factors (either conductive or severe unilateral hearing losses and hearing losses that did not have the high-frequency configuration).

The data were analyzed using SAS software (SAS Institute Inc, Cary, NC). Analysis of variance (ANOVA) was used to test for group differences in the covariates and thresholds. Multiple logistic regression analyses were performed for the estimation of odds ratios and to test for interactions. A stepwise procedure was used to determine which variables were to be included in the models. That is, at each step, the variable having the lowest significance level criterion (P value < 0.05) was added to the model, and values of probabilities >0.05 were removed from the model. Only the variables that added appreciably to the predictive power of the model remained in it. A method was developed for point and interval estimation for an arbitrary change of x units in the covariate.[22] The goal in selecting the value for x was to choose the value that offered the clearest indication of how the

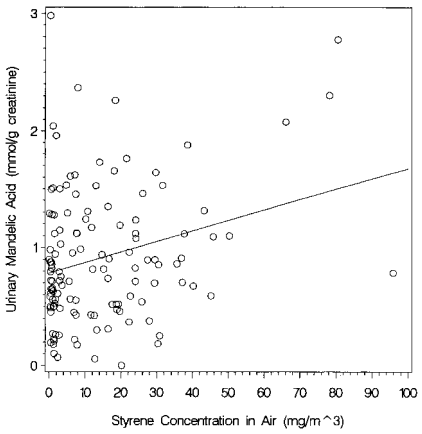

Fig. 1. Correlation between styrene in air and the biological determinant of styrene in urine—mandelic acid ($r = 0.27$, $P < 0.001$).

risk of the outcome being present changed with the variable in question.

Results

One-way ANOVAs compared the means of the response scores on the medical history, occupational and nonoccupational exposures, lifestyle factors, and present health and tested for differences between the four groups. The questions included data on smoking, diabetes, prior ear surgery, head injury, high fever, measles, high blood pressure, mumps, ear infections, history of hearing loss in the family, ototoxic medication use, and tinnitus. The only variable on which the groups differed statistically was tenure ($P < 0.001$; see Table 1); the noise-exposed workers had the shortest tenure.

Noise exposures exceeded recommended limits for 130 of the 313 studied workers. Styrene exposures never exceeded the Swedish recommended limits, which are among the world's lowest (90 mg/m^3, or 20 ppm). Results of the measurements of styrene in air and in urine were correlated and are displayed in Fig. 1 ($r = 0.27$, $P < 0.001$).

There was a higher prevalence of high-frequency hearing loss in the groups exposed to noise and styrene simultaneously (48%) and in those exposed to styrene alone (47%) compared with the other groups; prevalence was 33% in the nonexposed group and 42% in the noise-only-exposed group. The difference in prevalences, however, was not statistically significant.

In each group, mean thresholds at each frequency were calculated for each ear. Results are shown in Fig. 2. Significantly poorer thresholds at 2, 3, 4, and 6 kHz were observed in the styrene-exposed workers in both ears, compared with both of the two groups not exposed to styrene.

Analysis of Association Between Hearing Status and Exposure Conditions

The bilateral high-frequency hearing losses were examined as a binary outcome variable (normal hearing vs high-frequency hearing loss). The variables tested for inclusion in the model were age, occupational exposure data (including noise doses, current noise-equivalent 8-hour levels, lifetime noise estimates, and exposure indices for styrene), tenure, previous occupational exposure to noise or chemicals, exposure to nonoccupational noise, hearing protection use, smoking (number of cigarettes per day times the number of years of smoking), alcohol intake, medical history, and medications being taken. Some of the variables, such as age, tenure, and exposure data, were entered as continuous variables.

The only variables that met the significance level criterion for remaining in the model were age, tenure, styrene estimations, noise levels, and urinary mandelic acid levels. Table 2 shows the results of the final multiple logistic regression model, selected by the stepwise procedure, with the odds ratios for developing a hearing loss (calculated for the binaural classification of high-frequency hearing loss) and their 95% CIs. The odds ratio was calculated for each 1-year increase in age. The odds ratio was also estimated for an increased probability to develop a hearing loss with each increase of 1 mmol/g of creatinine in urine and 1 dB of noise exposure >85 dB. No significant statistical interaction other than additive was noted between styrene and noise.

The probability of the participants to develop a hearing loss based on levels of the biological marker urinary mandelic acid is shown in Fig. 3. The probability of the participants for developing a hearing loss based on noise exposure and age are shown in Figs. 4 and 5.

Discussion

All of the studied groups had an elevated prevalence of hearing loss when compared with groups in other epidemiological studies that used the same methods.[23–25] In Sweden, funding for work-related hearing loss

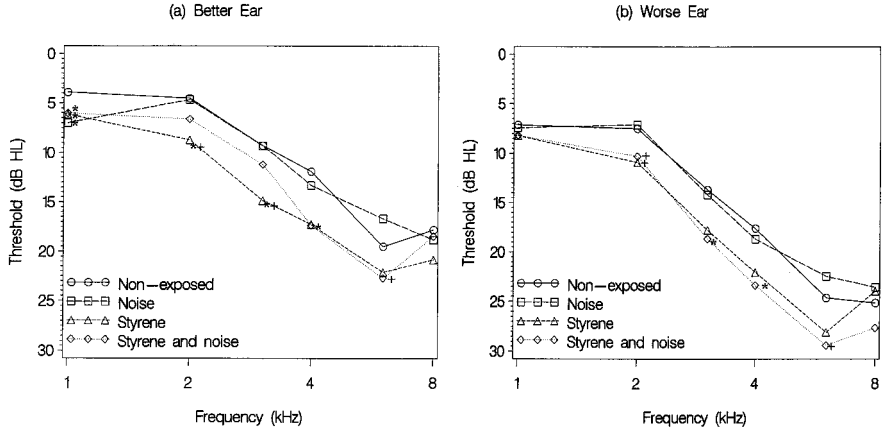

Fig. 2. Group mean hearing levels (dB HL) for the better (a) and worse (b) ears at frequencies between 1 and 8 kHz. Asterisks indicate frequencies that met the significance level criterion ($P < 0.05$) when compared with nonexposed workers, and the plus signs indicate frequencies that met the significance level criterion ($P < 0.05$) when compared with noise-exposed workers.

TABLE 2
Results of Multiple Logistic Regression Analyses for Occupational Hearing Loss

Variable	Beta	SE	Chi-Square	*P* Value	Odds Ratio (95% CI)
Intercept	−9.01	5.18	3.03	0.0818	. . .
Age	0.18	0.04	24.30	0.0001*	1.19 (1.11–1.28)
Current noise	0.17	0.08	4.57	0.0325*	1.18 (1.01–1.34)
Lifetime noise	−0.16	0.09	3.40	0.0652	0.85 (0.71–1.01)
Mandelic acid in urine	0.89	0.45	3.92	0.0478*	2.44 (1.01–5.89)
Lifetime styrene	−9.71	0.00	0.00	0.9739	1.00 (0.99–1.00)

* Indicate variables that met the significance level criterion ($P < 0.05$). Intercept values represent the proportion of hearing loss when all independent variables equaled zero.

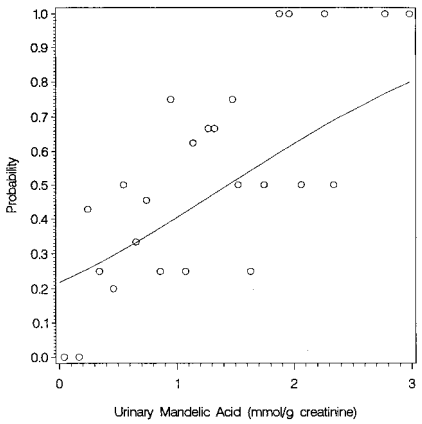

Fig. 3. Probability of developing a hearing loss by the biological determinant of styrene in urine (mmol of mandelic acid per g of creatinine). Each circle on the curve represents a predicted value for one or more individuals with a given urinary mandelic acid level.

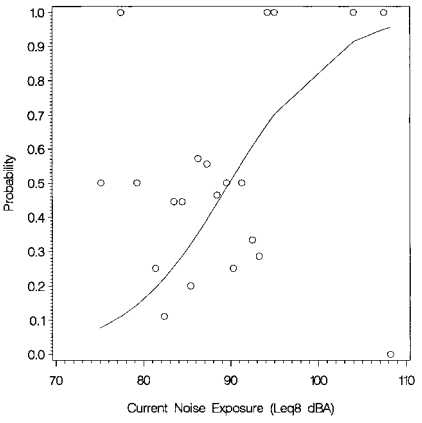

Fig. 4. Probability of developing a hearing loss by current noise exposure [in dB(A)]. Each circle on the curve represents a predicted value for one or more individuals with a given noise level.

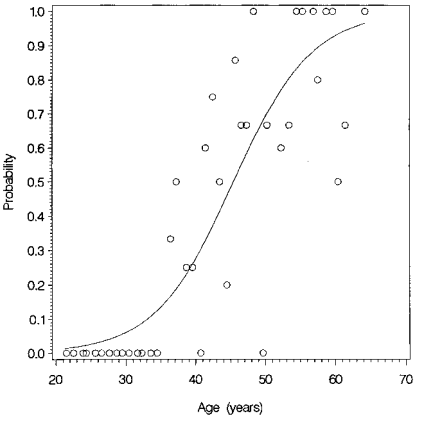

Fig. 5. Probability of developing a hearing loss by age. Each circle on the curve represents a predicted value for one or more individuals of a certain age.

research and occupational health services in general has been decreasing since the late 1980s, and an increase in cases of noise-induced hearing loss has been reported, following a decade (the 1970s) of success in controlling it.[26,27] In the 1990s, the annual case number of recognized noise-induced hearing loss in Sweden was ~1500, 8–9% of the total reported work-related diseases for ~5 of every 1000 employees.[28] In the present study, most of the companies did not have programs for noise reduction in place but instead relied primarily on supplying ear protection.

The difference in the prevalence of bilateral high-frequency hearing loss among the styrene-exposed (47%), styrene-and-noise-exposed (48%), and noise-exposed (42%) groups was not statistically significant from the control group, which could be explained by an inadequate sample size to detect the difference. Styrene-exposed workers had statistically significantly poorer pure-tone thresholds at the frequencies of 2, 3, 4, 6, and 8 kHz than the other studied groups. At the frequencies of 2, 3, and 8 kHz, the group exposed to styrene only had poorer thresholds than did those exposed to both agents. This observation might be the result of the variations in exposure histories and parameters. The group exposed to styrene alone was exposed to higher concentrations of the solvent than the group exposed to both agents, and they also had higher lifetime styrene estimates.

The percentage of hearing losses observed in the nonexposed group (33%) could be explained by reports from some of these workers that the workplace was noisier in the past. This information, however, could not be confirmed because of the lack of records. It is also likely that their noise exposure from previous jobs is associated with this observation (see mean values of previous noise exposure, in years, in Table 1).

This study corroborates earlier animal experiments that reported that chemicals, including styrene, can affect a broad band of frequencies from middle to high frequencies.[10,29] The current article is only the second to document the effects of solvents on the midaudiometric frequency of 2 kHz in humans. Similar observations have been reported by Sliwińska-Kowalska et al.[20]

In the present study, high-frequency hearing losses were examined by multiple logistic regression for the estimation of odds ratios. Age, current noise exposure, and the biological marker for styrene were the only variables that met the significance level criterion in the final

regression model. Researchers have studied extensively the increased prevalence of high-frequency hearing loss with age. (For a review on aging-related hearing loss, see Rosenhall and Pedersen.[30]) The odds ratio estimates obtained in the study reported here were 1.19 times greater for each increment of 1 year of age (95% CI, 1.11–1.28), 1.18 times greater for each increment of 1 dB >85-dB limit (95% CI, 1.01–1.34), and 2.44 times greater for each increment of 1 mmol (or for each increment of 152 mg) of mandelic acid per gram of creatinine in urine (95% CI, 1.01–5.89). The latter odds ratio indicates that both noise and styrene exposures were associated with the observed hearing losses. It is important to note that the mean styrene exposures were below the stringent Swedish recommended limits, which raises serious concerns.

Mandelic acid is a urinary metabolite of styrene. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a biological exposure index (BEI) of 800 mg of mandelic acid per gram of creatinine when the sampling occurs at the end of a work shift.[31] That value corresponds to an airborne concentration of styrene of 50 ppm, or 213 mg/m^3.[32] When the sampling time occurs before the next shift, the ACGIH recommends a BEI of 300 mg/g creatinine. In the present investigation, urine was collected for a period of 24 hours, so the results presented here include levels before, during, and after exposure.

In Sweden, biological exposure markers are not used as official exposure limits to styrene. In the present study, the correlation between styrene in air and mandelic acid in urine was low, but significant ($r = 0.27$, $P < 0.001$), despite the low exposure levels. The low correlation observed between styrene levels in air and mandelic acid in urine may be explained by the fact that urine collection, for practical reasons, started at the beginning of the work shift, reflecting in part the level of styrene exposure at the previous work shift. Urinary mandelic acid has been shown to correlate well with occupational exposure to styrene in field studies, also at low exposure levels.[33–35]

The association between the biological determinant of styrene and hearing loss raises serious concerns. The odds ratio for hearing loss estimated in this study is 2.44 for each 152 mg of mandelic acid per gram of creatinine. At the National Institute for Occupational Safety and Health (NIOSH)–recommended exposure limit of 300 mg/g creatinine of hippuric acid (which corresponds to ~19 ppm in air), the odds for hearing loss would be 4.88. The Swedish permissible exposure level for styrene of 20 ppm was not exceeded in any of the measurements performed by this investigation. Despite these low styrene exposures, pure-tone thresholds from exposed workers were significantly poorer than the thresholds for the other study groups. Their audiometric findings were found to be associated with the biological marker of styrene in urine. Similar findings have been reported previously.[19] High-frequency hearing thresholds were affected in workers exposed to low levels of styrene (2.9–28.9 ppm) and noise [69–76 dB(A)] for 5 years or more. This effect was associated with mandelic acid concentrations in urine.[19]

Even though styrene exposures were low in the studies discussed above, there is a possibility that peak, nontrivial exposures, current or past, may have contributed considerably in causing the losses. Thus, a lowering of limit-normalized levels might not eliminate the risk. More research on solvent-induced hearing losses is needed to address the adequacy of recommended limits, particularly in settings where combined exposures to chemicals and noise occur. The incorporation of peak measurements when setting exposure limits might be a desired approach for both noise and chemical exposures.

The present investigation found no statistical interactions between styrene and noise in causing a hearing loss, ie, no effect other than the additive was detected. In rats, styrene interacted synergistically with noise.[9,13] Despite careful attention to experimental control, human data are characterized by great individual variability (mainly from different susceptibilities and medical and exposure histories). This variability makes it challenging to separate the effects of each agent and to measure with precision the kind of interaction between two agents. Therefore, caution should be taken before generalizing the results of the present investigation to other populations.

Until now, occupational hearing-conservation programs have not taken chemical exposures into consideration, whether occupational and/or nonoccupational. The data from this study and other recent publications indicate such a need as part of the effort to prevent hearing loss. American public research institutions have taken an initial step in this direction. The National Occupational Research Agenda, the result of an inclusive consultation initiative, coordinated by the US NIOSH, has identified multiple exposures as a research priority for the occupational safety and health community.[1] The risk to hearing posed by combined exposures to noise and chemicals has been given as a specific example of a priority for investigation.

Additionally, in the NIOSH publications *Preventing Occupational Hearing Loss: A Practical Guide*[36] and the *Revised Criteria Document: Occupational Noise Exposure*,[4] an argument has been presented for broadening the scope of risk assessment and preventive initiatives. These documents also recommend that the term "occupational hearing loss" should not be a synonym for "noise-induced hearing loss." Moreover, it is advised that hearing-loss prevention programs take chemical exposures into account when monitoring a workplace for hazards, as-

sessing hearing, and controlling exposures.

The ACGIH, since its 1998 threshold limited values and BEIs publications, has gone a step beyond, including a note in its Noise section that states: "In settings where exposure to toluene, lead, manganese or *n*-butyl alcohol occurs, periodic audiograms are advised and should be carefully reviewed."[31] It also lists other chemicals under investigation. Such recommendations were followed by the US Army, which has included individuals exposed to chemicals in its hearing conservation programs since 1998.[37] With the increasing number of research groups involved in this area, data should be available in a few years that will allow recommendations to be formulated regarding ototoxicity exposure limits for chemicals and exposure limits for noise-chemical–combined exposures. Those recommendations would preferably also include hearing-loss prevention strategies that are not limited to controlling exposures to excessive noise levels.

Concluding Remarks

Evidence that occupational exposure to low levels of styrene can have an effect on the auditory system emphasizes the need to make workers and the occupational health community aware of the potential risk of chemically induced hearing loss. Until information is available on safe exposure levels to ototoxic chemicals such as styrene, the recommendation to include chemical-exposed workers in hearing-loss prevention programs seems appropriate, even when the noise levels are below recommended exposure limits.

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