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Original Article

A multicenter study on the audiometric findings of styrene-exposed workers

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Abstract

Objective: The objective of this study was to evaluate hearing loss among workers exposed to styrene, alone or with noise. *Design*: This cross-sectional study was conducted as part of NoiseChem, a European Commission 5th Framework Programme research project, by occupational health institutes in Finland, Sweden, and Poland. *Study sample*: Participants' ages ranged from 18–72 years (n = 1620 workers). Participants exposed to styrene, alone or with noise, were from reinforced fiberglass products manufacturing plants (n = 862). Comparison groups were comprised of workers noise-exposed (n = 400) or controls (n = 358). Current styrene exposures ranged from 0 to 309 mg/m^3, while mean current noise levels ranged from 70–84 dB(A). Hearing thresholds of styrene-exposed participants were compared with Annexes A and B from ANSI S3.44, 1996. *Results*: The audiometric thresholds of styrene exposed workers were significantly poorer than those in published standards. Age, gender, and styrene exposure met the significance level criterion in the multiple logistic regression for the binary outcome 'hearing loss' ($P = 0.0000$). Exposure to noise (<85 dBA $p = 0.0001$; ≥85 dB(A) $p = 0.0192$) interacted significantly with styrene exposure. *Conclusions*: Occupational exposure to styrene is a risk factor for hearing loss, and styrene-exposed workers should be included in hearing loss prevention programs.

Sumario

Objetivo: El objetivo de este estudio fue evaluar la pérdida auditiva en trabajadores expuestos a estireno, aisladamente o con ruido. *Diseño:* Se realizó este estudio transversal como parte del NoiseChem, Comisión Europea del 5º. Proyecto Marco de investigación, en institutos de salud ocupacional de Finlandia, Suecia y Polonia. *Muestra de estudio:* La edad de los participantes fue de 18–72 años (N=1,620 trabajadores). Los trabajadores (n = 862) estuvieron expuestos a estireno, solo o con ruido, en plantas de fabricación de productos de fibra de vidrio reforzada. Los grupos de comparación fueron trabajadores expuestos a ruido (n= 400) y los de un grupo control (n = 358). Las exposiciones reales a estireno variaron de 0 a 309 mg/m3, mientras que los niveles reales de ruido, variaron de 80–84 dB(A). Se compararon los niveles de audición de los participantes expuestos a estireno con los de los anexos A y B de ANSI S3.44, 1996. *Resultados:* Los umbrales audiométricos de los trabajadores expuestos a estireno, fueron significativamente más pobres que los que se han publicado como estándar. La edad, el género y la exposición a estireno, cubrieron los criterios de niveles de significatividad de la regresión logística múltiple para los resultados binarios de la "perdida auditiva" ($P = 0.0000$). La exposición a ruido (<85 dB(A) $p = 0.0001$; ≥85 dB(A) $p = 0.0192$) interactuó significativamente con la exposición a estireno. *Conclusiones:* La exposición ocupacional a estireno es un factor de riesgo de pérdida auditiva por lo que los trabajadores expuestos a estireno deben ser incluidos en programas de prevención de pérdidas auditivas.

Key Words: Pure-tone audiometry; Otologically unscreened; Noise; Hearing loss.

The ototoxicity of therapeutic drugs has been a concern in the fields of pharmacology and otolaryngology for two centuries. In comparison, the ototoxicity of chemicals found in the environment from contaminants in air, food, or water, and in the workplace has only in the past 20 years been a topic of systematic investigation for toxicologists, audiologists, and other health professionals. Before that, isolated reports as early as the 1800s could be found linking exposure to metals and hearing loss (Schacht & Hawkins, 2006). Reviews on the effects of solvents and the implications for the practice of audiology were published in recent years (Fuente & McPherson, 2006; Morata, 2007).

One of the most studied organic solvents in recent years is styrene (Hoet & Lison, 2008). Once the ototoxicity of toluene and its synergistic interaction with noise was demonstrated and confirmed, attention turned to styrene because of its structural similarity to toluene (Rebert et al, 1983; Campo et al, 2003; Pryor et al, 1984). Styrene has been shown to be an even more potent ototoxicant than toluene in rats (Loquet et al, 1999) in causing permanent and progressive damage to the auditory

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Abbreviations

GC	Gas chromatography
TWA	Time-weighted average

system. Several experiments have revealed that noise interacts with styrene in a synergistic manner (Campo et al, 2003; Lataye et al, 2000; Makitie et al, 2003).

Multiple clinical and occupational studies have examined the hearing of workers exposed to styrene, alone or in combination with excessive noise (Muijser et al, 1988; Sass-Kortsak et al, 1995; Moller et al, 1990; Calabrese et al, 1996; Morioka et al, 1999, 2000; Morata et al, 2002; Hoffmann et al, 2006; Johnson et al, 2006; Mascagni et al, 2007; Triebig et al, 2009). No studies exist of workers exposed to styrene alone in a totally quiet environment. But in several studies, it has been possible to investigate groups of workers exposed to styrene when the noise levels were below 85 dB(A), levels not typically considered harmful (OSHA, 1981). These studies have shown that occupational exposure to low levels of styrene can affect the human auditory system, even when noise exposure is not considered excessive (Morioka et al, 1999; Morata et al, 2002; Sliwinska-Kowalska et al, 2003; Johnson et al, 2006; Treibig et al, 2008). Some questions were raised about the human reports, given that the exposure levels reported to have an effect in humans were lower than those previously reported to induce an effect in experimental animals (Lawton et al, 2006). Integrating information on the acute toxicity (which result from a single or a series of exposures in a short period of time) of organic solvents into predictive relationships between exposure and effect in humans (mostly exposed to repeated exposures, often at lower levels, to a substance over a longer time period, of months or years) is often challenging. Risk data are usually derived from experimental animals whose sensitivity to the chemical relative to humans is unknown, the mode of action of the chemical is rarely understood, and dose-response estimates can be modified by several factors (Bushnell et al, 2007). The difference in the lowest concentration necessary to cause an effect in humans and rats has not been understood until recently. Researchers have demonstrated that by making experimental animals active during chemical exposure, the lowest concentration of styrene needed to elicit an auditory effect was much reduced (Lataye et al, 2005). It has been suggested that auditory effects of solvents may have been observed at lower concentrations in humans, because humans are generally exposed to solvents in combination with a multitude of other factors (additional risk factors, repeated exposures, high physical demands, etc.), whereas animal experiments typically involve short-term isolated solvent exposure in quiescent subjects.

The available evidence has raised the issue of the need for and challenges involved in risk assessment and the determination of (1) the lowest exposure concentration at which adverse hearing effects occur, and (2) the exposure concentration at which no adverse effects occur. Animal data provide more straightforward information than human data. In rats, the lowest adverse effect concentration was found after exposure to 200 mg/kg by gavage, which resulted in styrene blood levels estimated to correspond to approximately 250 ppm exposure by inhalation (Chen et al, 2007). Exposure to 400 ppm styrene simultaneously with 85 dB(A) octave band noise was associated with significant auditory changes (Lataye et al, 2005). However, if rats were made to be active during styrene exposure, thus increasing the solvent uptake, auditory effects were found at the 300 ppm exposure level (Lataye et al, 2005). Regarding occupational exposures, more information is needed regarding the auditory risk from exposure to styrene in the workplace to elucidate not only safe exposure concentrations, but also exposure scenarios that should be of concern, and when further preventive action would be recommended.

As part of NoiseChem, a research project funded by the European Commission 5th Framework Programme (Prasher et al, 2002), this multicenter, cross-sectional study was designed to evaluate the occurrence of hearing loss among workers exposed to styrene, alone or in concert with noise, and to determine whether the auditory thresholds of styrene-exposed workers are different from those of men and women in the general population, using frequency by frequency comparisons.

Methods

The research team consisted of representatives from six different institutions. Data collection was under the responsibility of four research centers located in three countries (the Swedish National Institute for Working Life, Finnish Institute for Occupational Health, the Polish Institute of Occupational Medicine and Environmental Health, and the Nofer Institute of Occupational Medicine, Poland). In each country, the collection of data involved several sites, which varied from very small to large facilities. Across all studied facilities, most of the measured exposures were within the local permissible limits (12–20 ppm or 50–105 mg/m^3). Three of the research centers have published reports on the analysis of their part of the combined database used in this investigation (Morata et al, 2002; Johnson et al, 2006; Sliwinska-Kowalska et al, 2003; Toppila et al, 2006).

In each of the centers, researchers had access to different equipment and capabilities, so agreement was reached through consensus on a minimal set of common protocols to be used for the measurements and for the merging of the data. The same minimal set of questions was translated into the local languages, and information was gathered about work history, non-occupational solvent and noise exposure, life style factors, and medical history. At each of the study facilities, a different audiological test battery was used (including one or more of the following tests: distortion product otoacoustic emissions, psychoacoustic modulation transfer function, interrupted speech, speech recognition in noise and cortical response audiometry, gaps-in-noise, posturographic measurements, frequency pattern test and duration pattern test). In the present study, we are only reporting the results of the pure-tone audiometric testing. Exposure assessment included data collected from interviews, company records, and site measurements of styrene and noise levels for different job categories.

The project was approved by the ethics committees of each of the institutes involved in the data collection portion of the study.

Participants

The study population was composed of 1620 workers (1276 male, 312 female respondents, 32 who did not provide gender information), and their ages ranged between 18 and 63 years. Of the initial cohort who agreed to be in the study, 1404 workers completed all steps of the investigation. The participants who had held jobs which involved styrene exposure for at least six months, alone (n = 423) or in combination with noise (n = 268) were included in the styrene-exposure group, and were all from manufacturing plants of reinforced fiberglass products (n = 691). Comparison groups were comprised of workers either exposed to noise alone (n = 359) or controls (n = 354) and worked with fiberglass products and in other various industries (metal, wood products, docks, and office work). Each research center contributed participants for all the studied exposure conditions (exposed and non-exposed). At each plant, workers from specific departments were (according to their exposure estimates) invited to participate and encouraged by their management to do so. Only 3–5% declined the opportunity.

Styrene exposure assessment

To determine potential exposure levels to styrene, time-weighted average (TWA) exposure evaluations were conducted on 85% to 100% of the subjects exposed to styrene and on sub-samples of subjects from the other groups for control purposes only. For the workers whose personal styrene exposure was not assessed, the mean value of styrene concentrations from workers who had the same jobs and were doing the same tasks in the same environment was used in the analyses.

Passive samplers were used to collect full-shift air samples. The sampling device was positioned as close as possible to the breathing zone of the worker. The adsorption tube samples were sealed and stored in a freezer for later GC (gas chromatography) analysis. Two successive samples were collected for each worker, and the average collection time took 3 hours and 50 minutes each (never shorter than 80% of an 8-hour working shift). For further details on the equipment used, see Morata et al, 2002; Sliwinska-Kowalska et al, 2003; Toppila et al, 2006 (in Sosnowiec, Poland, the same equipment was used as in Finland). Self-report of personal protection use can be perceived by workers as sensitive information, so self-reported use does not necessarily mean effective use. Given the observation from evaluators indicating that the use of respiratory protection equipment was low and/or inconsistent among exposed workers, self-reported use of respirators was not entered in the analysis.

Noise exposure assessment

Noise exposure was assessed by personal exposure measurements using Brüel and Kjær sound pressure level meters and dosimeters in Sweden and Łódź, Poland; Larson Davis equipment was used in Finland; and Svan sound pressure level meters and dosimeters were used in Sosnowiec, Poland. All equipment was calibrated annually, but calibration was checked on every measurement day, before measurements were performed. Exposure assessments were calculated individually, based on 8-hour level equivalent dosimeter measurements, $L_{eq\ 8hours}$ dB(A). The 3-dB exchange rate was used in all calculations. Full-shift noise dosimetry was performed for all different work tasks. For the workers who did not have personal noise dosimetry performed, a mean value was calculated from the noise exposures levels obtained from at least 75% of the workers doing the same work tasks in the same environment and used in the analyses. Self-report of personal protection use can be perceived by workers as sensitive information, so self-reported use does not necessarily mean effective use (Neitzel & Seixas, 2005). Given the observation from evaluators indicating that the use of hearing protection equipment was low and/or inconsistent among exposed workers in all participating countries, information on the use of these devices was not entered in the analysis. Because of the differences in the exposure records maintained in the participating countries, we were not able to perform the calculation of cumulative lifetime exposure estimates for either noise or styrene.

The characteristics of the study population regarding their age, tenure, and current exposures to the studied agents are presented in Table 1 by research center. Styrene exposure levels were the lowest in Sweden and Finland, and their variability was also smaller. In the Scandinavian centers, chemical exposures were restricted to styrene, sometimes in combination with acetone. In Sosnowiec 15 workers reported ethylbenzene co-exposure, while in Łódź it was reported that approximately 40 workers had co-exposure to toluene, but no other details were available. Noise levels did not vary significantly across centers.

We compared the styrene exposure levels with the study population divided into noise groups. This variable dichotomized to be 1 if the noise exposure was greater than or equal to 85 dB(A), or 0 if the noise exposure was less than 85 dB(A). The group exposed to styrene and noise levels below 85 dB(A) had higher levels of styrene exposure. Their mean styrene exposure level was 43 mg/m^3 (SD 50, range 0.001 to 308 mg/m^3), while the groups that were also noise exposed had a mean exposure level of 40 mg/m^3 (SD 51, range 0. 001 to 245 mg/m^3).

Pure-tone audiometric testing

Hearing examinations were performed at least 16 hours after the last exposure to noise to minimize the detection of temporary threshold shifts. All testing was conducted in soundproof booths (Sweden/Finland, and in some locations in Poland) or quiet rooms (remaining locations in Poland). In every study center, measurements were conducted to ensure that the requirements of ISO 8253–1 for audiometric testing environments were met (ISO, 1989a). In case the testing at that location lasted longer than one day or if it involved different shifts,

Table 1. Characterization of the study population (n = 1620). Mean values and range (within parenthesis) for age, tenure, and current noise and styrene exposures. For styrene, ranges and mean values of exposures results include only the results from exposed groups.

Variable	*Mean age, in years ± SD (range)*	*Mean tenure, in years ± SD (range)*	*Mean current noise level ± SD (range) in dB(A)*	*Mean styrene in air ± SD, in mg/m^3 (range)*
Finland	39 ± 12	11 ± 9	82 ± 7	7 ± 10
n = 279	(18–63)	(1–42)	(54–95)	(0.001–43)
Sweden	43 ± 11	15 ± 10	84 ± 6	13 ± 17
n = 313	(20–65)	(1–39)	(70–100)	(0.03–96)
Poland/Sosnowiec	31 ± 11	10 ± 9	82 ± 7	68 ± 61
n = 267	(18–63)	(1–41)	(70–97)	(6.1–245)
Poland/Lødz	36 ± 10	11 ± 9	80 ± 10	61 ± 51
n = 729	(20–72)	(1–53)	(59–99)	(3.6–309)

Note: To convert concentrations in air (at 25 °C) from ppm to mg/m^3: mg/m^3 = (ppm) × (molecular weight of the compound)/(24.45). For styrene: 1 ppm = 4.26 mg/m^3.

sound levels were measured before each 8-hour period of testing. Daily calibration checks were performed immediately before testing of subjects, while acoustic calibration of the equipment according to ISO 389 was performed before data collection (ISO, 1989b).

Otoscopy was performed to screen for conditions that would exclude a person from the study, i.e., external otitis or perforated tympanic membrane. For pure-tone audiometry, a Technical Audiological Measurement Processor (TAMP3, Unit of Technical Audiology, TA, Karolinska Institute) was used in Sweden, Madsen Midimate 622 in Finland, a Madsen Orbiter audiometer was used by the Sosnowiec group, and the Interacoustics AC40 audiometer was used by the Łódź laboratory. Headphones type TDH-39 with MX41AR cushion were used in Sweden, Finland and Sosnowiec, while in Łódź, a special Peltor H7A headphone cover was worn to help attenuate external noises.

The research center in Sweden used a fixed-frequency Békésy method for audiometry controlled by the individual being tested, while three centers (Finland, Łódź, and Sosnowiec) used conventional manual octave pure-tone audiometry at fixed audiometric frequencies (0.5 to 8 kHz). Békésy audiometry is known to give slightly lower (0.8 to 2.5 dB difference) and more reliable hearing thresholds, because in pure-tone audiometry steps used in the testing are larger, i.e. 5 dB compared with 1 dB (Knight, 1966a, b; Harris, 1980). Since the thresholds of the participants from each study center were not contrasted against one another, this difference in measurement technique was considerable acceptable.

Each audiogram was evaluated for hearing loss. An audiogram was considered as normal if thresholds did not exceed 25 dB HL (hearing level) at any tested frequency. If it revealed a notch at one of the frequencies between 3 and 6 kHz (a notch was defined as a recovery of 10 dB or more at the higher frequency adjacent to the poorest threshold at 3, 4, or 6 kHz), the audiogram was classified as 'notched' hearing loss. A non-occupational category was included to account for those hearing losses that could not be attributed to occupational factors (either conductive or severe unilateral hearing losses, or hearing losses that did not have the high-frequency notch).

Statistical methods

The pure-tone audiometry thresholds were also compared with Annexes A and B of ANSI 3.44 (ANSI, 1996). Annex A represents a highly screened population for ear pathology, while B represents an unscreened population. Annex A represents either ear while Annex B represents better ears, so we used better ear data from the study groups for the comparisons. The proportion of persons with thresholds worse than the median (50th percentile) and 90th percentile reference values were calculated. t-tests were carried out to determine whether the proportions were significantly different from 0.50 for the median and 0.10 for the 90th percentile.

Stepwise logistic regression was used to determine which interactions to include in the final model. The regression model included indicator variables for research center (Sweden, Finland, Sosnowiec, and Łódź), as well as variables gender, age, noise, and styrene. These variables were forced into the models. Noise was entered in the logistic regression both as a continuous as well as a dichotomous variable. The interactions included age × gender, noise (continuous) × gender, styrene × gender, age × noise group (dichotomous), age × styrene, and noise group (dichotomous) × styrene. An interaction was included in the final model if it remained in one of the stepwise models. The criterion to enter or leave the stepwise models was $P = 0.05$.

The final logistic regression model included classification variables for research center and gender, continuous variables for age, noise, and styrene, and noise group (dichotomous) × styrene interaction.

Table 2. Proportions above the median (50th percentile) and 90th percentile of age-correlated hearing levels from ANSI 3.44 Annex A, highly screened for ear pathology of a normal population and standard error of pooled study participants who were exposed to styrene alone or in combination with noise (n = 628 male and 63 females).

Test frequency in kHz	*Proportion above the median*	*Std error*	*Pr > |t| H_0: π = 0.5*	*Proportion above the median*	*Std error*	*Pr > |t| H_0: π = 0.5*	*Proportion above the 90th percentile*	*Std error*	*Pr > |t| H_0: π = 0.5*	*Proportion above the 90th percentile*	*Std error*	*Pr > |t| H_0: π = 0.5*
	Better ear			*Worse ear*			*Better ear*			*Worse ear*		
Males												
0.5	0.71	0.030	0.0001*	0.86	0.024	0.000*	0.31	0.03	0.0001*	0.49	0.03	0.0001*
1.0	0.78	0.016	0.0001*	0.90	0.012	0.0001*	0.42	0.02	0.0001*	0.59	0.02	0.0001*
2.0	0.72	0.018	0.0001*	0.87	0.013	0.0001*	0.24	0.02	0.0001*	0.44	0.02	0.0001*
3.0	0.75	0.019	0.0001*	0.88	0.014	0.0001*	0.24	0.02	0.0001*	0.47	0.02	0.0001*
4.0	0.75	0.017	0.0001*	0.92	0.011	0.0001*	0.29	0.02	0.0001*	0.51	0.02	0.0001*
6.0	0.82	0.015	0.0001*	0.95	0.009	0.0001*	0.34	0.02	0.0001*	0.59	0.02	0.0001*
8.0	0.68	0.019	0.0001*	0.86	0.014	0.0001*	0.13	0.01	0.0048*	0.34	0.02	0.0001*
Females												
0.5	0.67	0.087	0.1100	0.90	0.055	0.0001*	0.17	0.07	0.3433	0.27	0.08	0.0517
1.0	0.67	0.060	0.0071*	0.83	0.048	0.0001*	0.25	0.05	0.0071*	0.41	0.06	0.0001*
2.0	0.59	0.062	0.1676	0.73	0.056	0.0001*	0.19	0.05	0.0745	0.30	0.06	0.0010*
3.0	0.51	0.069	0.8923	0.74	0.061	0.0003*	0.23	0.06	0.0339*	0.38	0.07	0.0001*
4.0	0.65	0.060	0.0154*	0.79	0.051	0.0001*	0.17	0.05	0.1269	0.32	0.06	0.0005*
6.0	0.81	0.049	0.0001*	0.92	0.034	0.0001*	0.16	0.05	0.2104	0.40	0.06	0.0001*
8.0	0.55	0.063	0.3821	0.80	0.049	0.0001*	0.10	0.04	0.8988	0.24	0.05	0.0132*

*Asterisks indicate significant differences.

Table 3. Proportions above the median (50th percentile) and 90th percentile of age-correlated hearing levels from ANSI 3.44 Annex B, unscreened for ear pathology of a normal population and standard error of pooled study participants exposed to styrene, alone or in combination with noise (n = 628 male and 63 females).

Test frequency in kHz	*Proportion above the median*	*Std error*	*Pr > /t/ H_0: π = 0.5*	*Proportion above the median*	*Std error*	*Pr > /t/ H_0: π = 0.5*	*Proportion above the 90th percentile*	*Std error*	*Pr > /t/ H_0: π = 0.5*	*Proportion above the 90th percentile*	*Std error*	*Pr > /t/ H_0: π = 0.5*
	Better ear			*Worse ear*			*Better ear*			*Worse ear*		
Males												
0.5	0.35	0.036	0.0001*	0.50	0.038	0.8793	0.06	0.02	0.0205*	0.15	0.02	0.0421*
1.0	0.75	0.019	0.0001*	0.85	0.015	0.0001*	0.14	0.01	0.0031*	0.31	0.02	0.0001*
2.0	0.71	0.019	0.0001*	0.86	0.015	0.0001*	0.13	0.01	0.0643	0.28	0.02	0.0001*
3.0	0.49	0.023	0.6775	0.68	0.021	0.0333*	0.03	0.01	0.0001*	0.13	0.01	0.0500*
4.0	0.39	0.021	0.0001*	0.64	0.021	0.0001*	0.05	0.01	0.0001*	0.12	0.01	0.1711
6.0	0.33	0.020	0.0001*	0.58	0.021	0.0001*	0.05	0.01	0.0001*	0.15	0.01	0.0030*
Females												
0.5	0.17	0.069	0.0001*	0.47	0.093	0.7216	0.03	0.03	0.0549	0.10	0.05	1.0000
1.0	0.69	0.059	0.0017*	0.85	0.045	0.0001*	0.23	0.05	0.0220*	0.34	0.06	0.0002*
2.0	0.60	0.063	0.1285	0.77	0.053	0.0001*	0.15	0.04	0.3206	0.27	0.06	0.0034*
3.0	0.48	0.070	0.7845	0.67	0.066	0.0111*	0.12	0.04	0.7323	0.27	0.06	0.0088*
4.0	0.61	0.062	0.0752	0.81	0.050	0.0001*	0.11	0.04	0.7512	0.27	0.06	0.0034*
6.0	0.34	0.060	0.0099*	0.62	0.062	0.0411*	0.03	0.02	0.0040*	0.13	0.04	0.5014

*Asterisks indicate significant differences.

All calculations were done with SAS®, (Version 9.1 SAS Institute, Inc., Cary, North Carolina). The stepwise regression was done with PROC LOGISTIC. The final model was done with PROC LOGISTIC.

Results

The comparison of proportions of styrene-exposed study participants (excluding controls and those only exposed to noise) differing from the median thresholds found in Annexes A and B of ANSI 3.44, showed that the study group had significantly greater proportions of poorer thresholds. The results are displayed in Tables 2 and 3.

Table 2 displays t-tests results indicating that the proportions of styrene-exposed males with thresholds worse than the median (50th percentile) and 90th percentile reference values of a highly screened population (Annex A) were significantly different for all test frequencies, for both ears. For women, this was only true for their worse ear. Still, their thresholds were significantly worse in several test frequencies. Table 3 displays t-tests results showing that the proportions of styrene-exposed males with thresholds worse than the median (50th percentile) and 90th percentile reference values of an unscreened population (Annex B) were significantly differently for most (not all) test frequencies, for both ears. For women, the statistically significant differences are restricted to fewer test

Table 4. Results of the final model of the multiple logistic regression analyses for hearing loss, including the variables research center, age, gender, styrene and noise measurements, and noise (both as a continuous and dichotomous variable). Odds ratio and respective 95% confidence intervals (CI) are also given. Odds ratios were estimated for increased probability to develop hearing loss for each 1-year increase in age, for each increase of 1 mg/m^3 of styrene, and being of male gender.

Variable	*β*	*SE*	*χ^2*	*p*	*Odds ratio (95% CI)*
Intercept	−5.72	0.841	43.37	0.0000	N.A.
Finland (vs. Sweden)	0.12	0.168	0.54	0.4610	1.28 (0.79–2.10)
Łódź (vs. Sweden)	−0.04	0.102	0.13	0.7152	1.09 (0.79–1.5)
Sosnowiec (vs. Sweden)	0.04	0.149	0.08	0.7766	1.18 (0.76–1.86)
Age	0.08	0.007	158.98	0.0000*	1.08 (1.07–1.10)
Gender (M vs. F)	0.57	0.092	38.65	0.0000*	1.09 (1.07–1.10)
Noise	0.01	0.009	1.28	0.2579	1.01 (0.99–1.03)
Styrene, noise < 85 dB(A)	0.0186	0.0024	59.75	0.0000*	1.0188 (1.0140–1.0236)
Styrene, noise ≥ 85 dB(A)	0.0055	0.0024	5.49	0.0192*	1.0055 (1.0009–1.0102)
Styrene by noise group	−0.0131	0.0032	16.57	0.0000*	

Abbreviations: SE = Standard error; CI = Confidence interval. Intercept values represent the proportion of hearing loss when all independent variables equaled zero. Asterisks indicate significant differences. Note: To convert concentrations in air (at 25°C) from ppm to mg/m^3: mg/m^3 = (ppm) × (molecular weight of the compound)/(24.45). For styrene: 1 ppm = 4.26 mg/m^3.

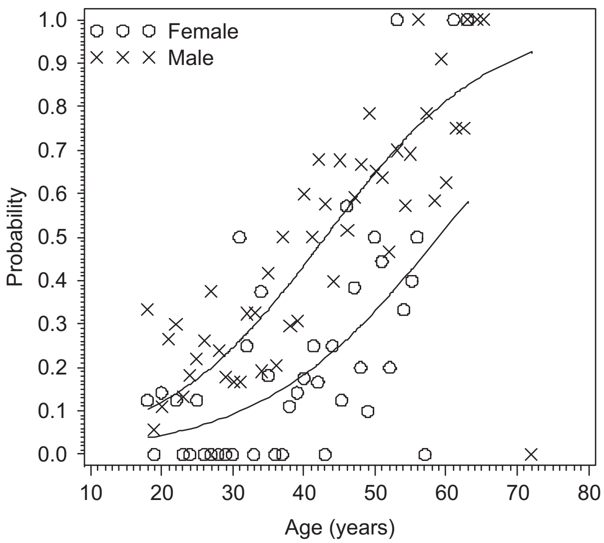

Figure 1. Predicted probability of the study participants developing a notched hearing loss based on age and gender. The points represent proportions and are calculated for each year of age. The curves in these graphs are the predicted probabilities from the logistic regression models joined by straight lines.

frequencies. In summary, the styrene-exposed participants had poorer hearing thresholds then reference data, throughout the frequency range tested. As expected, the difference is more pronounced when the comparison is made with a highly screened dataset.

Following the thresholds comparison, audiometric results were classified and bilateral notched hearing losses were examined as a binary outcome variable (normal hearing vs. notched hearing loss). The variables tested for inclusion in the model were research center (study location), age, gender, occupational exposure data (current noise-equivalent 8-hour levels, and exposure concentrations for styrene), and tenure. Some of the variables, such as age, tenure, and exposure data, were entered as continuous variables. Noise exposure was also entered as a dichotomous variable according to whether the noise exposure level was below (<) or above (≥) 85 dB(A).

Age, male gender, and styrene exposure measured in air were the variables that met the significance level criterion in the multiple logistic regression for the binary outcome 'hearing loss' ($P = 0.0000$). The probability of hearing loss was greater among older participants as well as for males. We tested for interaction between the exposure variables, as well as between them and age and gender. No significant interaction was found for age or gender and the exposure variables. Noise exposure was not significant as a variable by itself, but interacted significantly, modifying the effect of the styrene exposure (noise <85 dB(A), $p = 0.0001$; noise ≥ 85 dB(A), $p = 0.0192$). Table 4 shows the results of the final multiple logistic regression models, selected by the stepwise procedure, with the odds ratios for developing hearing loss (calculated for the binaural classification of notched hearing loss), and 95% confidence intervals (CI). A method was developed for point and interval estimation for an arbitrary change of x units in the covariate.

Using the logistic regression results, the probability of the participants' developing a notched hearing loss (as a binary variable) based on age and gender are shown in Figure 1. The probability of the participants developing hearing loss based on the levels of styrene exposure and its interaction with noise are shown in Figures 2a and b. In these graphs showing the probability of hearing loss, the points represent proportions and are calculated at 1-unit intervals for noise, 10-unit intervals for styrene, and for each year of age. The curves in these graphs are the predicted probabilities from the logistic regression models joined by straight lines.

Figure 2a shows that as styrene concentration increases, so does the probability of hearing loss. As indicated in Table 4, noise exposure and styrene exposures interact to increase the probability of hearing loss. Figure 2b shows that the angle of the probability curve is modified by noise exposure. When mean noise exposure levels were equal or greater than 85 dB(A) TWA, the effects from noise dominated.

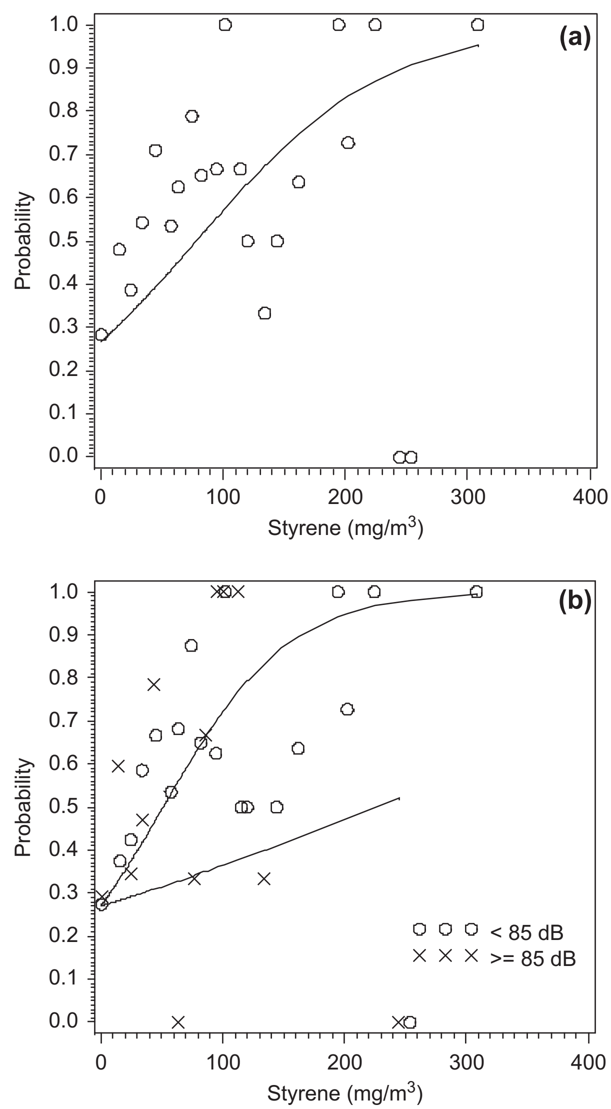

Figure 2. (a and b). a: The predicted probability of the participants developing a notched hearing loss based on styrene exposure levels (all subjects included, regardless of noise levels). b: The predicted probability of the participants developing a hearing loss based on styrene exposure levels and its interaction with noise. In these graphs, showing the probability of hearing loss, the points represent proportions and are calculated for one unit intervals for noise and ten unit intervals for styrene. The curves in these graphs are the predicted probabilities from the logistic regression models joined by straight lines.

Discussion

The results of this multicenter, cross-sectional study of workers from Sweden, Finland, and Poland confirm an association between hearing thresholds and occupational exposure to styrene and noise, as well as age and gender. Styrene exposure (measured in air) was associated with poorer thresholds than predicted by an individual's age (when compared with ANSI S3.44 Annexes A and B). The differences were noted across all tested frequency range. Similar findings have been reported for previous studies on solvent effects on hearing (for a review see Johnson & Morata, 2010). This portion of the data analysis, however, just indicated that the styrene-exposed study participants had poorer hearing thresholds than those found in the published standards, but it gave no information on what risk factors were associated with the observed differences.

Multiple logistic regression was performed to identify which risk factors were associated with an increased probability of developing hearing loss. The recorded noise levels were equivalent across study centers, and the means varied between 80 and 84 dB(A). No statistically significant effect of such noise levels on hearing was observed, except when in combination with styrene. This study is in agreement with other field occupational studies that detected a deleterious effect of styrene on hearing (Morioka et al, 1999, 2000; Mascagni et al, 2007; Triebig et al, 2008). This study, however, is the first to observe a statistically significant interaction between noise and styrene in causing hearing loss in humans. Statistically significant interactions between noise and styrene had only been reported previously with experimental animals (Lataye et al, 2000). For study participants who were exposed to noise levels equal or greater than 85 dB(A), the noise effect dominated. Similar observations have been reported in previous studies. For example, Rabinowitz et al (2008) reported that risk associated with mixed solvent exposure has been reported to be smaller for employees who reported shooting or hunting.

The group exposed to styrene alone was exposed to higher concentrations of the solvent than the group exposed to both noise and styrene. The study was conducted in facilities where noise and styrene measurement results were below the local exposure limit values, with few sample results in excess of these limits. It is important to remember however that participants could have been exposed to higher styrene concentrations in the past, and that exposure to peaks of high styrene levels could explain the observed effects. Moreover, in both study locations in Poland, styrene exposure occurred in combination with other ototoxicants in a few instances, and information about those exposures was not complete nor entered in the analysis. Because of the potential co-exposure to other ototoxicants in the fiberglass products manufacturing industry, caution is suggested when extrapolating the findings of this study to other industries in which styrene exposures occur. We tested for research center or location effects, and we did not find it to be a significant risk factor. In other words, the differences in probability of hearing loss were explained by age, gender, and styrene and noise exposures, and not by the country where participants worked.

Robust animal evidence on styrene intoxication routes (Lataye et al, 2001) provides biologically plausible mechanisms to explain the interaction between noise and styrene. In the present study, the precise identification of the contribution of each factor was not possible, because of lack of complete information on exposure histories and other relevant parameters of the studied populations, a weakness inherent to studies with human subjects.

It is possible that the observed effect of styrene exposure is due to exposure misclassification or some form of bias, or both. Some degree of misclassification is almost always present when the results of exposure measurements for a job category are extrapolated to individuals, but such misclassification tends to be nondifferential.

Age and gender are important factors to consider when examining hearing disorders, and both were significantly associated with hearing loss in this study. The effects of noise and age are challenging to differentiate but seem to be additive, or perhaps synergistic. Animal experiments report that early noise exposure (in young animals) has a measurable impact on hearing later in the exposed animal's life (Kujawa & Liberman, 2006; Ohlemiller et al, 2000). Similarly, young rats are more vulnerable to the effects of styrene (Campo et al, 2003). Still, it is not clear whether that is the case also with humans, and if so, what would make a young person more susceptible. Hearing can decline with age, but the healthy individual who has not been exposed to ototraumatic agents may have normal hearing beyond the age of 65. The median hearing level across the frequencies of 1, 2, 3, and 4 kHz for non-noise exposed 60-year-old males is 17 dB HL, and 12 dB HL for females (ANSI 3.44, 1996). Gender and race seem also to be associated with the susceptibility to hearing loss, as studies conducted with groups with similar jobs and exposures have indicated that Caucasian males constitute the group with poorer thresholds and higher prevalence of noise-induced hearing loss, while African American females have the lowest prevalence of hearing loss (Szanto & Ionescu, 1983; Driscoll & Royster, 1984). The potential interaction between gender and hearing loss is not fully understood. There may be a real difference in susceptibility, or it may be that the apparent gender-related differences can be attributed to differences in exposure histories and/or compliance with HPD use (Lusk et al, 1997; Reed et al, 2006).

Occupational exposure limits for styrene vary from 12 ppm (50 mg/m^3) in Europe to 100 ppm (215 mg/m^3) in the US for time-weighted averages of exposure (Johnson & Morata, 2010). In humans, exposure levels of styrene at the time field studies were conducted varied from a mean of 4 ppm up to approximately 50 ppm. Two human studies did not find any significant effects that could be attributed to styrene exposure (Sass-Kortsak et al, 1995; Hoffman et al, 2006). In both of these studies, the current styrene exposure was around 25 ppm. Poorer hearing thresholds were reported for workers exposed to styrene as measured by the biological marker for styrene, mandelic acid, compared with nonexposed age- and gender-matched controls (Morata et al, 2002; Johnson et al, 2006; Morioka et al, 1999; Sliwinska-Kowalska et al, 2003). The lowest exposures that resulted in a significant hearing loss of exposed workers, when compared with non-exposed controls, were in the 3.5 to 22 ppm range (Morata et al, 2002; Johnson et al, 2006; Morioka et al, 1999; Sliwinska-Kowalska et al, 2003).

Although our data indicate that low exposures to noise and styrene are associated with an increased probability of hearing loss, they do not allow us any attempt on dose-response calculations or to speculate about a safe styrene exposure concentration to prevent hearing loss. At the moment, the best information for the risk assessment of styrene comes from studies with experimental animals (Lataye et al, 2005). Based on their findings, scientists from the Institut National de Recherche et de Sécurité (INRS) in France proposed lowering the occupational exposure limit (permissible time-weighted average) for styrene from 50 to 30 ppm, in addition to the compulsory use of hearing protectors for 8-hour noise exposure to 80 dB(A) (European Agency for Safety and Health at Work, 2009).

Preventive strategies used to protect workers from the effects of noise exposure will not completely protect workers from the effects of chemical exposure. When evidence that chemicals in the workplace can affect hearing is considered, then hearing loss prevention initiatives may be needed even in workplaces where noise exposure does not exceed 85 dB(A).

The preferred method of hearing loss prevention is the control or elimination of hazards at its source through engineering controls or substitution. Some alternatives for controlling styrene exposure in fiberglass reinforced products manufacturing can be found in the literature (Valladares et al, 2005) and in the website http://www2.cdc.gov/nioshtic-2/.

Since 1998, the American Conference of Governmental Industrial Hygienists in its (TLVs® and BEIs®) publication (ACGIH, 1998) includes 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.' It also lists other aims to develop specific recommendations and disseminate information addressing hearing loss prevention strategies that are not limited to exposures to excessive noise levels. A similar recommendation can be found in the *Australia-New Zealand AS/NZS 1269:2005 Occupational Noise Management/Informative Appendix on Ototoxic Agents*, suggesting hearing tests for those exposed to ototoxic agents.

Also since 1998, the US Army started requiring consideration of ototoxic chemical exposures for inclusion in a hearing conservation program, particularly when in combination with marginal noise exposures. More recently, the US Army recommends audiometric monitoring for workers whose airborne exposures are at 50 percent of the most stringent criteria for occupational exposure limits to otoxicants (http://chppm-www.apgea.army.mil/documents/FACT/51-002-0903.pdf).

The 2003 European Community (EC) directive on noise (2003/10 EC noise, Article 4 of Section II) requires that the interaction between noise and ototoxic chemicals be taken into account in the risk assessment of exposed populations, but it does not give any details on how to implement their recommendations. Some suggestions were offered by researchers in the field in consensus meetings (Morata, 2003; Sliwinska-Kowalska et al, 2007) and extensive reviews (European Agency for Safety and Health at Work, 2009; Johnson & Morata, 2010).

Conclusions

The results suggest that occupational exposure to styrene in fiberglass product manufacturing is a risk factor for notched hearing loss. Clinicians involved in the evaluation of an individual's hearing or in the analyses of audiometric databases should gather information on risk factors, usually through an interview or questionnaire. It is important that these professionals obtain exposure history information on environmental or occupational exposures to ototoxic chemicals such as styrene and on the use of protective equipment. The lowest styrene workplace exposure levels which have been associated with hearing loss range from 3.5 to 22 ppm. Countries which allow higher exposure levels should re-examine their permissible exposure limit based on styrene ototoxicity data. In the meantime, workers in styrene-exposed jobs should be evaluated for possible over-exposure due to variable exposure scenarios depending on job task, intermittent peak exposures, and dermal exposure. According to our results, minimizing exposures to noise and styrene and the inclusion of styrene-exposed workers in hearing loss prevention programs is warranted.

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