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ORIGINAL ARTICLE

Association of organic solvents and occupational noise on hearing loss and tinnitus among adults in the U.S., 1999–2004

Amanda M. Staudt[1,2] · Kristina W. Whitworth[2] · Lung-Chang Chien[3] · Lawrence W. Whitehead[4] · David Gimeno Ruiz de Porras[2,5,6]

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Abstract

Purpose Exposure to organic solvents and noise may be causal agents in the development of hearing loss and tinnitus. The objectives of the present study were to examine the association of organic solvents with hearing loss and tinnitus and to assess the interaction of organic solvent and occupational noise exposure on hearing loss and tinnitus.

Methods A secondary data analysis of data from the National Health and Nutrition Examination Survey and Occupational Information Network (O*NET) among a study population ranging from 1085 to 2471 study participants from 1999 to 2004. Multiple multivariate logistic regression models were used to assess the associations of individual organic solvent exposures as measured by blood biomarkers (1,4-dichlorobenzene, benzene, ethylbenzene, styrene, toluene, *o*-xylene, and *m*-/*p*-xylene) with self-reported hearing loss, audiometrically assessed hearing loss, and self-reported tinnitus. Models were adjusted for age, gender, race/ethnicity, diabetes, non-occupational noise exposure, smoking, and income. Organic solvents found to be statistically significantly associated with the outcome after adjusting for covariates were tested for interaction with occupational noise exposure.

Results Solvent exposure was not statistically significantly associated with self-reported tinnitus. Benzene (OR 1.43, 95% CI 1.15–1.78), ethylbenzene (OR 1.24, 95% CI 1.02–1.50), and toluene (OR 1.27, 95% CI 1.06–1.52) concentrations were statistically significantly associated with increased adjusted odds of high-frequency hearing loss. No statistically significant interaction was observed between these solvents and occupational noise on high-frequency hearing loss.

Conclusions We found no evidence of an association between organic solvents and tinnitus; however, there was evidence of an association between organic solvent exposure and prevalence of high-frequency hearing loss.

Keywords Blood biomarkers · Hearing loss · NHANES · Occupational noise · Organic solvents · Tinnitus

✉ Amanda M. Staudt
amanda.m.staudt2.ctr@mail.mil

[1] Systems of Care for Complex Patients (SCCP) Task Area, US Army Institute of Surgical Research, 3698 Chambers Pass, JBSA Fort Sam Houston, San Antonio, TX 78234, USA

[2] Southwest Center for Occupational and Environmental Health, Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health in San Antonio, The University of Texas Health Science Center at Houston, San Antonio, TX, USA

[3] Epidemiology and Biostatistics Program, Department of Environmental and Occupational Health, School of Community Health Sciences, University of Nevada, Las Vegas, USA

[4] Southwest Center for Occupational and Environmental Health, Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, The University of Texas Health Science Center at Houston, Houston, TX, USA

[5] Center for Research in Occupational Health (CISAL), Universitat Pompeu Fabra, Barcelona, Spain

[6] CIBER of Epidemiology and Public Health, Barcelona, Spain

Introduction

In the United States (US), hearing loss affects approximately 48 million adults (Hearing Loss Association of America 2015a), while tinnitus affects approximately 50 million adults (Shargorodsky et al. 2010). Hearing loss is the partial or complete inability to hear, and tinnitus is the sense of hearing ringing or other noise, when there is no other observable source (Nadol 1993; Olishifski 1988). Known causes of tinnitus and hearing loss include noise, presbycusis (i.e., age-related hearing loss), obstruction by physical agent, and otosclerosis (i.e., deafness produced by growth of bone in the inner ear) (Hearing Loss Association of America 2015b; Mayo Clinic 2013; Mayo Clinic Staff 2018). Other causes of hearing loss include health conditions (e.g., disease, infection, medication use, and tumors), genetics (e.g., malformation of the inner ear, Ménière's disease), or external contact (e.g., head trauma) (Hearing Loss Association of America 2015b; Mayo Clinic Staff 2018). Exposure to certain industrial chemicals, such as organic solvents (i.e., carbon-based substances capable of dissolving or dispersing other substances) has also been suggested as a causal agent in the development of hearing loss and tinnitus (Centers for Disease Control and Prevention 2018a). Several studies have documented the ototoxicity of 1,4-dichlorobenzene, benzene, ethylbenzene, styrene, toluene, *o*-xylene, and *m*-/*p*-xylene (Campo et al. 2001; Fuente et al. 2013a; Gagnaire and Langlais 2005; Morata et al. 1997, 2011; Pryor et al. 1987; Risk Assessment Information System 1997; Risk Assessment Information System 1998; Waniusiow et al. 2009).

Research has shown noise can cause mechanical or metabolic injury (Nordmann et al. 2000) which is caused by overstimulation of stereocilia of hair cells and leads to cell death (Waters 1999). Additionally, cell death increases metabolic activity and may initiate the formation of free radicals (e.g., reactive oxygen species). The production of free radicals is associated with cellular injury and thought to be part of the underlying mechanism for noise-induced hearing loss (Henderson et al. 2006; Morata 2010). The mechanism for organic solvent-induced hearing loss is less clear. In the cochlea, exposure to organic solvents has produced cochlear lesions leading to hearing loss (Campo et al. 2001). In the central auditory pathway, organic solvents can: (1) inhibit the auditory efferent system (Campo et al. 2007; Lataye et al. 2007); and (2) block the protective middle ear reflex (Maguin et al. 2009), which leads to hearing loss. Though noise may cause tinnitus by causing damage to the auditory hair cells (Leaver et al. 2015), the potential mechanism for organic solvent-induced tinnitus is unclear.

Limitations of previous studies include a scarcity of information on the association of individual organic solvents with hearing loss in human studies and limited research available on the association of organic solvent exposure and tinnitus. Moreover, a comparison of previous studies also shows inconsistent results in the association of some individual organic solvents with hearing loss (Fuente et al. 2013a; Morata et al. 2011; Schaper et al. 2008; Triebig et al. 2009). Furthermore, there is difficulty in comparing the effect of organic solvent and noise exposure on hearing loss and tinnitus as definitions often vary from study to study. Thus, the objectives of the present study were to examine the association of a series of organic solvents (i.e., 1,4-dichlorobenzene, benzene, ethylbenzene, styrene, toluene, *o*-xylene, and *m*-/*p*-xylene) with hearing loss and tinnitus and to assess the effect of the interaction of exposure to those organic solvents and occupational noise on hearing loss and tinnitus.

Methods

We conducted a secondary analysis of data collected by the National Health and Nutrition Examination Survey (NHANES), a nationally representative cross-sectional survey conducted by the US Centers for Disease Control and Prevention (CDC) (Centers for Disease Control and Prevention 2018b). For all NHANES participants, questionnaire data, including hearing/audiometry and demographic covariates, were collected. Additionally, audiometric testing and measurement of blood concentrations of environmental contaminants, including solvents, were conducted on a random subsample of participants (Centers for Disease Control and Prevention 2018b). The present analyses were restricted to individuals aged 20–59 years who participated in NHANES during 1999–2004 who had available blood concentrations of the following organic solvents: 1,4-dichlorobenzene, benzene, ethylbenzene, styrene, toluene, *o*-xylene, and *m*-/*p*-xylene. The final sample size available for each organic solvent varied due to laboratory quality control measures (Blount et al. 2006).

Audiometric hearing loss was assessed in NHANES through a pure-tone air conduction threshold test at seven frequencies (0.5, 1, 2, 3, 4, 6, and 8 kHz) over an intensity range of 10–120 dB (Centers for Disease Control and Prevention 2018b). In the present study, we computed the pure-tone average by averaging the air-conduction thresholds at 0.5, 1, 2, and 4 kHz. We defined hearing loss as a pure-tone average threshold change greater than or equal to 25 dB in either ear, which is consistent with the definition used by the World Health Organization (WHO 2015).

Self-reported hearing loss and tinnitus were also assessed in NHANES using questionnaires. Study participants were asked "which statement best describes your hearing (without a hearing aid)?" In the present study, study participants

were categorized as having self-reported hearing loss if they responded to the question with "a little trouble, a lot of trouble, or deaf". NHANES participants were also asked "in the past 12 months, have you ever had ringing, roaring, or buzzing in your ears?" In the present study, participants who responded yes to this question were classified as having self-reported tinnitus.

As part of NHANES data collection, the concentrations of 1,4-dichlorobenzene, benzene, ethylbenzene, styrene, toluene, *o*-xylene, and *m*-/*p*-xylene in human blood were analyzed using solid-phase microextraction with gas chromatography and bench top quadrupole mass spectrometer (Centers for Disease Control and Prevention 2018b). Solvent concentrations below the limit of detection (LOD) (i.e., LOD 1,4-dichlorobenzene = 0.120, benzene = 0.024, ethylbenzene = 0.024, *m*-/*p*-xylene = 0.034, *o*-xylene = 0.049, styrene = 0.030, and toluene = 0.025) were reported as the LOD divided by the square root of 2 (Centers for Disease Control and Prevention 2018b). The distribution of organic solvent concentrations was right-skewed. Though we explored several transformations of these outcome variables, including a log transformation, we found the cubic root transformation provided the best normalization based on plotting the distribution of the transformed outcome variables.

We obtained data from the Occupational Information Network (O*NET) from March 2002 to July 2015 to attribute occupational noise in the present study. O*NET is a national source of detailed information on job tasks and hazards, including estimated noise exposures for occupations based on standard occupation codes (SOCs) (O*NET Resource Center 2015). O*NET occupational noise exposure scores are based on self-reported assessments to the following question: "In your current job, how often are you exposed to sounds and noise levels that are distracting and uncomfortable?," with the following response options coded from 1 to 5 points, respectively: never, once a year or more but not every month, once a month or more but not every week, once a week or more but not every day, and every day.

In the present study, we linked O*NET noise exposure estimates with the occupational codes for each participant's longest held job. The longest held job was ascertained in NHANES by the following question: "thinking of all the paid jobs or businesses you ever had, what kind of work were you doing the longest?" Because there is not a direct crosswalk between NHANES and O*NET occupational codes, we used a crosswalk process involving the following steps: (1) NHANES occupational codes to 1990 Census codes (US Census Bureau 2018); (2) 1990 Census codes to the 2000 Census codes (US Census Bureau 2003); (3) 2000 Census codes to the Standard Occupational Classification (SOC) system (National Crosswalk Service Center 2015); and, (4) SOC codes to O*NET-SOC codes (National Crosswalk Service Center 2015). Following prior research (Choi et al. 2012), we assigned the average cumulative O*NET-SOC noise score to each NHANES occupational category. We subsequently categorized occupational noise into high and low exposure groups based on the median noise level for all participants [median score = 2.84 (interquartile range (IQR) = 2.59–3.67]. These mean O*NET noise scores represent the probability that an individual in a given occupational category is exposed to "distracting and uncomfortable sounds and noise". The higher the score, the greater the probability that individuals in a given occupational category are exposed daily to "distracting and uncomfortable noise levels".

The following NHANES variables were examined as covariates: age (years), gender (male/female), non-occupational noise exposure (yes/no), diabetes (yes/no), race/ethnicity (Hispanic, non-hispanic black, non-hispanic white, other), smoking (yes/no), total household income (< \$20,000/≥ \$20,000), and use of ototoxic medication (yes/no). In NHANES, the use of prescription medication was assessed using the following question: "In the past month, have you used or taken medication for which a prescription is needed?" Participants who responded "yes" were further asked to provide the drug name(s). For the present study, we defined use of ototoxic medications as self-reported use of aminoglycosides, antineoplastic drugs, nonsteroidal anti-inflammatory drugs, or loop diuretics during the past month as recorded in by NHANES. Personal and secondary smoking status was collected in NHANES using the following questions: "Have you ever tried cigarette smoking, even 1 or 2 puffs?" and "Does anyone who lives here smoke cigarettes, cigars, or pipes anywhere inside this home?" We classified participants as smokers if they responded positively to either of these questions. We classified diabetes using NHANES data on self-reported physician diagnosis (i.e., "Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?"). Participants were classified as exposed to non-occupational noise if they reported (in NHANES) that they have "outside of work, ever been exposed to firearms noise for an average of at least once a month for a year" or "ever been exposed to other types of loud noise, such as noise from power tools or loud music, for an average of at least once a month for a year," where loud noise means noise so loud that they had to speak in a raised voice to be heard.

The inclusion and exclusion criteria for this study are shown in Fig. 1. Note, the age range of 20–59 years was chosen because blood concentrations of the organic solvents of interest were only available among this age group during the study years. In addition, we excluded individual organic solvent measurements for 39 participants for whom the reported solvent concentration exceeded the calibrated range of the assay as these measured concentrations may be imprecise. In each analysis, the range of final sample sizes

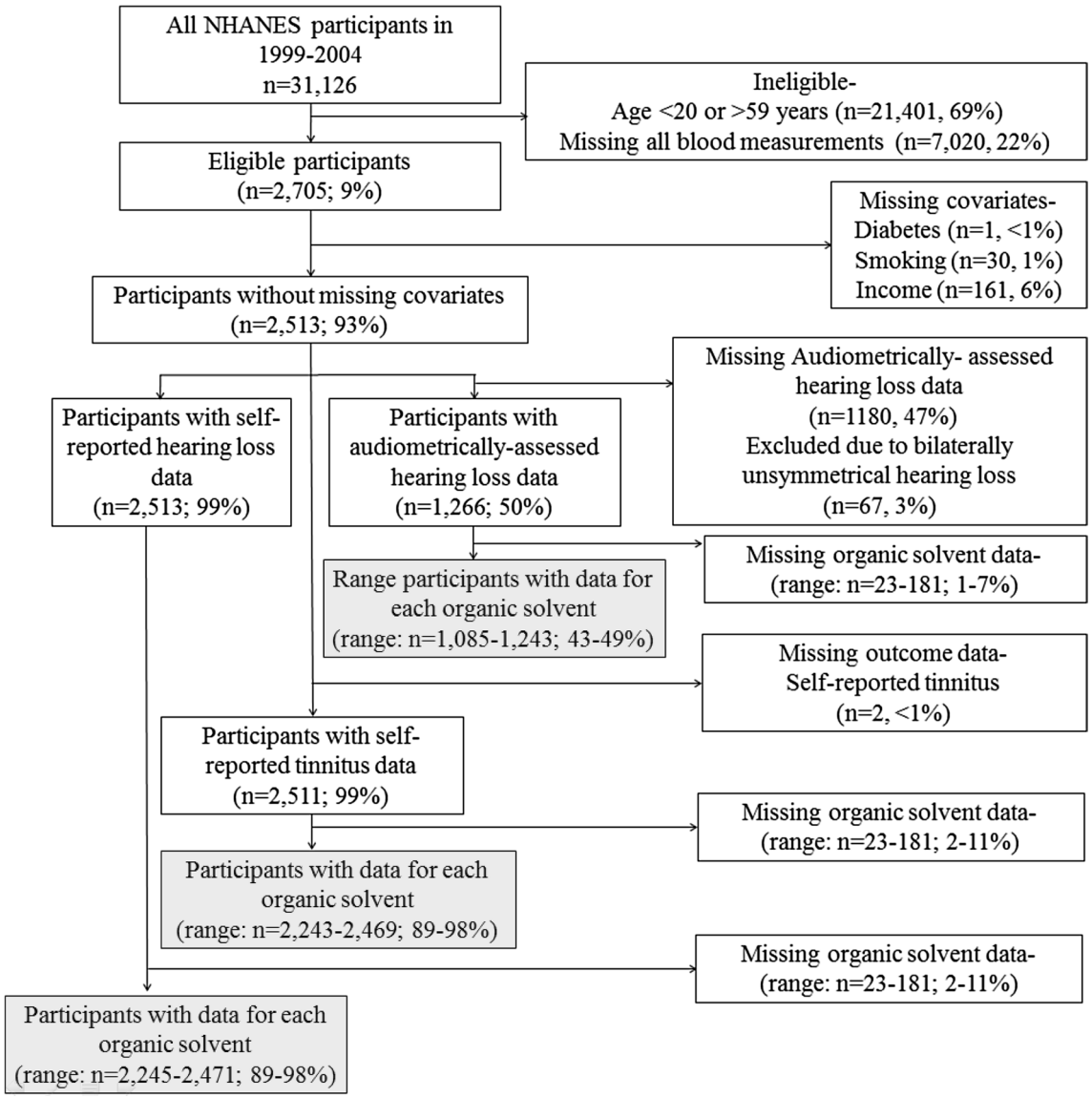

Fig. 1 Flow chart of study inclusion among US adults in NHANES, 1999–2004

were as follows: 2245 to 2471 participants for self-reported hearing loss, 2243 to 2469 for self-reported tinnitus, and 1085 to 1243 for audiometrically assessed hearing loss.

To compare demographic characteristics by hearing loss and tinnitus, χ^2 and t tests were used, as appropriate. We constructed separate multivariate logistic regression models to examine associations between each individual organic solvent and each of the three outcomes (i.e., self-reported hearing loss, audiometrically assessed hearing loss, and self-reported tinnitus). Covariates were identified using the following model selection process to identify the best fit model. First, we constructed a full model, where the outcome variable was toluene and the exposure variable was audiometrically assessed hearing loss, including all covariates (i.e., age, gender, non-occupational noise exposure, diabetes, race/ethnicity, smoking, income, and use of ototoxic medications) and identified those which were statistically significantly (i.e., $p < 0.05$) associated with the outcome (i.e., age, gender, non-occupational noise exposure, diabetes, and race/ethnicity). These covariates were then included in a reduced model. Finally, every possible combination of remaining variables (i.e., smoking, income, and use of ototoxic medications) was added to the reduced model, and the Akaike information criterion of these models was compared. Based on this criterion, smoking and income were added to the reduced model to create the final adjusted model. Model selection was repeated for every combination of the exposure variables (i.e., 1,4-dichlorobenzene, benzene, ethylbenzene, styrene, toluene, *o*-xylene, and *m*-/*p*-xylene) and outcome (i.e., self-reported hearing loss,

audiometrically assessed hearing loss, and self-reported tinnitus) to ensure similar selection of covariates. We present odds ratios (ORs) representing odds of hearing loss per an IQR increase in organic solvent concentration. The organic solvents found to be statistically significantly associated with any of the three outcomes (i.e., hearing loss, audiometrically assessed hearing loss, and self-reported tinnitus) were tested for interaction with occupational noise exposure, by including an interaction term between the solvent and occupational noise in each of the final adjusted models.

As previous studies have used different definitions of hearing loss, we conducted a sensitivity analysis using a different definition of audiometrically assessed hearing loss to explore the robustness of our findings. In this sensitivity analysis, high-frequency hearing loss was defined as average loss in air conduction pure-tone threshold at 3, 4, 6, 8 kHz greater than 15 dB in either ear, while low-frequency hearing loss was defined as average loss in air conduction pure-tone thresholds at 0.5, 1, 2 kHz greater than 15 dB in either ear (Shargorodsky et al. 2011). All analyses were completed using Stata (StataCorp 2015). In all the analyses, p values below 0.05 were declared to be statistically significant.

Results

Table 1 summarizes demographic characteristics of the study participants by hearing loss and tinnitus. The mean age of study participants was 38.2 years [standard deviation (SD) = 11.1, range = 20–59]. A slightly more than half of the participants were female (53%), half were non-hispanic white (50%), a majority had an income equal to or over $20,000 (81%), only a smaller proportion of participants had recently used ototoxic medication (4%), less than a quarter

Table 1 Demographic characteristics among US adults in NHANES, 1999–2004, by hearing loss and tinnitus status

	Self-reported hearing loss		Audiometrically assessed hearing loss		Self-reported tinnitus	
	Yes	No	Yes	No	Yes	No
Age (years), mean ± SD		$p < 0.001$		$p < 0.001$		$p = 0.011$
	42.7 ± 10.6	37.1 ± 10.9	47.3 ± 10.2	37.0 ± 10.8	39.5 ± 11.3	37.8 ± 11.0
Gender, *n* (%)		$p < 0.001$		$p < 0.001$		$p = 0.412$
Male	272 (56.7)	923 (45.4)	68 (68.0)	526 (45.1)	289 (49.1)	906 (47.1)
Female	208 (43.3)	1,110 (54.6)	32 (32.0)	640 (54.9)	300 (50.9)	1016 (52.9)
Race/ethnicity, *n* (%)		$p < 0.001$		$p = 0.005$		$p = 0.002$
Hispanic	107 (22.3)	542 (26.7)	23 (23.0)	295 (25.3)	133 (22.6)	514 (26.7)
Non-hispanic white	295 (61.5)	955 (47.0)	65 (65.0)	583 (50.0)	334 (56.7)	916 (47.7)
Non-hispanic black	60 (12.5)	447 (22.0)	7 (7.0)	237 (20.3)	98 (16.6)	409 (21.3)
Other	18 (3.8)	89 (4.4)	5 (5.0)	51 (4.4)	24 (4.1)	83 (4.3)
Income, *n* (%)		$p = 0.857$		$p = 0.822$		$p = 0.053$
< $20,000	92 (19.2)	397 (19.5)	19 (19.0)	211 (18.1)	131 (22.2)	358 (18.6)
≥ $20,000	388 (80.8)	1636 (80.5)	81 (81.0)	955 (81.9)	458 (77.8)	1564 (81.4)
Ototoxic medication, *n* (%)		$p = 0.031$		$p = 0.007$		$p = 0.038$
No	451 (94.0)	1955 (96.2)	90 (90.0)	1118 (95.9)	555 (94.2)	1849 (96.2)
Yes	29 (6.0)	78 (3.8)	10 (10.0)	48 (4.1)	34 (5.8)	73 (3.8)
Smoker, *n* (%)		$p < 0.001$		$p = 0.024$		$p < 0.001$
No	338 (70.4)	1611 (79.2)	70 (70.0)	928 (79.6)	414 (70.3)	1533 (79.8)
Yes	142 (29.6)	422 (20.8)	30 (30.0)	238 (20.4)	175 (29.7)	389 (20.2)
Diabetes, *n* (%)		$p = 0.033$		$p = 0.003$		$p = 0.060$
No	447 (93.1)	1941 (95.5)	89 (89.0)	1115 (95.6)	551 (93.5)	1835 (95.5)
Yes	33 (6.9)	92 (4.5)	11 (11.0)	51 (4.4)	38 (6.5)	87 (4.5)
Occupational noise exposure, *n* (%)		$p = 0.034$		$p = 0.001$		$p = 0.018$
Low	111 (44.9)	506 (52.5)	13 (28.3)	302 (54.2)	151 (45.5)	466 (53.1)
High	136 (55.1)	458 (47.5)	33 (71.7)	255 (45.8)	181 (54.5)	412 (46.9)
Non-occupational noise exposure, *n* (%)		$p < 0.001$		$p = 0.001$		$p < 0.001$
No	274 (57.1)	1486 (73.1)	55 (55.0)	827 (70.9)	331 (56.2)	1428 (74.3)
Yes	206 (42.9)	547 (26.9)	45 (45.0)	339 (29.1)	258 (43.8)	494 (25.7)

p values for age differences from *t* of Student's test, -values for all other variables from Chi-squared tests

were smokers (22%), and a small group were diabetic (5%). Regarding noise exposures, near a quarter of the participants had high exposure to noise in their jobs (23%) and near a third were classified as exposed to non-occupational noise (30%). Except where indicated, compared to non-cases, among cases of hearing loss and tinnitus the mean age was higher (i.e., cases were older), there were more males (although not for tinnitus), more non-hispanic whites and fewer non-hispanic blacks, more people who used ototoxic medication, smokers and people with diabetes (although not for tinnitus), people with high exposure to occupational noise and people exposed to non-occupational noise. All these differences were statistically significant. No difference by income level was observed.

Table 2 displays the median blood concentration of organic solvents for study participants by hearing loss and tinnitus. The lowest median blood concentration of organic solvents was in styrene (0.02 ng/mL, IQR = 0.02, 0.06) and the highest median values were in 1,4-dichlorobenzene (0.14 ng/mL, IQR = 0.08, 0.42), and *m*-/*p*-xylene (0.14 ng/mL, IQR = 0.09, 0.22). The median blood concentration of benzene (0.04 [IQR = 0.02, 0.11] vs. 0.03 [IQR = 0.02, 0.09], $p < 0.001$) and ethylbenzene (0.04 [IQR = 0.02, 0.061] vs. 0.03 [IQR = 0.02, 0.05], $p = 0.048$) varied for those with self-reported hearing loss as compared to those without. In addition, the median blood concentration of benzene (0.06 [IQR = 0.03, 0.11] vs. 0.03 [IQR = 0.02, 0.09], $p = 0.023$) varied for those with audiometrically assessed hearing loss as compared to those without.

The relation between blood concentrations of organic solvents and odds of hearing loss and tinnitus is shown in Table 3. The associations between audiometrically assessed hearing loss and benzene [OR 1.50; 95% confidence interval (CI) 1.15–1.94], ethylbenzene (OR 1.31; 95% CI 1.04–1.67), and toluene (OR 1.29; 95% CI 1.04–1.60) were statistically significant. In addition, the associations between self-reported hearing loss and benzene (OR 1.30; 95% CI 1.15–1.47), ethylbenzene (OR 1.20; 95% CI 1.06–1.36), and toluene (OR 1.17; 95% CI 1.04–1.31) were statistically significant, and the association between self-reported tinnitus and benzene (OR 1.16; 95% CI 1.03–1.31) and ethylbenzene (OR 1.14; 95% CI 1.01–1.28) were statistically significant. None of the ORs in the analysis between organic solvents and hearing loss (audiometrically assessed and self-reported) and self-reported tinnitus remained statistically significant ($p \geq 0.05$) after adjusting for covariates. Hence, no analysis was conducted on the interaction of occupational noise with organic solvent exposure and self-reported hearing loss, audiometrically assessed hearing loss or self-reported tinnitus.

Table 2 Median (IQR) blood concentration of organic solvent concentrations among adults in NHANES, 1999–2004, by hearing loss and tinnitus status

	Organic solvent (ng/mL)	Yes		No		*p* value
		n	Median (IQR)	*n*	Median (IQR)	
Self-reported hearing loss	1,4-Dichlorobenzene	439	0.08 (0.08, 0.39)	1806	0.14 (0.08, 0.43)	0.496
	Benzene	453	0.04 (0.02, 0.11)	1862	0.03 (0.02, 0.09)	< 0.001
	Ethylbenzene	443	0.04 (0.02, 0.06)	1842	0.03 (0.02, 0.05)	0.048
	m-/*p*-Xylene	461	0.14 (0.10, 0.24)	1955	0.14 (0.09, 0.22)	0.062
	o-Xylene	472	0.03 (0.03, 0.06)	1999	0.03 (0.03, 0.05)	0.278
	Styrene	433	0.03 (0.02, 0.07)	1862	0.02 (0.02, 0.06)	0.673
	Toluene	463	0.13 (0.06, 0.34)	1942	0.12 (0.06, 0.26)	0.067
Audiometrically assessed hearing loss	1,4-Dichlorobenzene	82	0.08 (0.08, 0.40)	1003	0.14 (0.08, 0.46)	0.854
	Benzene	90	0.06 (0.03, 0.11)	1040	0.03 (0.02, 0.09)	0.023
	Ethylbenzene	86	0.04 (0.03, 0.07)	1039	0.03 (0.02, 0.05)	0.281
	m-/*p*-Xylene	92	0.17 (0.10, 0.26)	1116	0.14 (0.09, 0.23)	0.226
	o-Xylene	99	0.04 (0.03, 0.06)	1144	0.03 (0.03, 0.06)	0.921
	Styrene	87	0.04 (0.02, 0.08)	1066	0.02 (0.02, 0.06)	0.801
	Toluene	99	0.17 (0.08, 0.37)	1106	0.13 (0.06, 0.27)	0.185
Self-reported tinnitus	1,4-Dichlorobenzene	520	0.12 (0.08, 0.40)	1723	0.14 (0.08, 0.43)	0.580
	Benzene	537	0.04 (0.02, 0.11)	1776	0.03 (0.02, 0.09)	0.163
	Ethylbenzene	533	0.03 (0.02, 0.06)	1750	0.03 (0.02, 0.05)	0.231
	m-/*p*-Xylene	564	0.14 (0.09, 0.23)	1850	0.14 (0.09, 0.22)	0.243
	o-Xylene	578	0.03 (0.03, 0.05)	1891	0.03 (0.03, 0.06)	0.930
	Styrene	540	0.03 (0.02, 0.07)	1753	0.02 (0.02, 0.06)	0.571
	Toluene	561	0.14 (0.06, 0.30)	1842	0.11 (0.06, 0.27)	0.449

Table 3 Association between organic solvent exposure and hearing loss and tinnitus among US adults in NHANES, 1999–2004

Organic solvent (ng/mL)	Self-reported hearing loss		Audiometrically assessed hearing loss		Self-reported tinnitus	
	OR (95% CI)[a]		OR (95% CI)[a]		OR (95% CI)[a]	
	Crude	Adjusted[b]	Crude	Adjusted[b]	Crude	Adjusted[b]
1,4-Dichlorobenzene	0.93 (0.86, 1.00)	1.00 (0.93, 1.08)	0.96 (0.82, 1.13)	1.04 (0.87, 1.24)	0.96 (0.90, 1.03)	1.01 (0.94, 1.08)
Benzene	1.30 (1.15, 1.47)	1.11 (0.96, 1.29)	1.50 (1.15, 1.94)	1.20 (0.85, 1.68)	1.16 (1.03, 1.31)	0.98 (0.85, 1.13)
Ethylbenzene	1.20 (1.06, 1.36)	0.99 (0.86, 1.15)	1.31 (1.04, 1.67)	1.02 (0.73, 1.41)	1.14 (1.01, 1.28)	0.98 (0.85, 1.12)
m-/*p*-Xylene	1.10 (0.99, 1.22)	0.95 (0.84, 1.07)	1.20 (0.97, 1.48)	0.95 (0.73, 1.23)	1.07 (0.97, 1.18)	0.98 (0.88, 1.10)
o-Xylene	1.06 (1.00, 1.14)	1.00 (0.93, 1.08)	1.09 (0.96, 1.24)	0.98 (0.82, 1.17)	1.01 (0.95, 1.08)	0.97 (0.90, 1.04)
Styrene	1.05 (0.96, 1.15)	0.96 (0.85, 1.09)	1.06 (0.93, 1.20)	0.94 (0.72, 1.25)	1.03 (0.95, 1.12)	0.95 (0.84, 1.06)
Toluene	1.17 (1.04, 1.31)	0.96 (0.84, 1.10)	1.29 (1.04, 1.60)	1.00 (0.77, 1.30)	1.09 (0.98, 1.22)	0.93 (0.82, 1.06)

[a]Odds ratio (OR) and confidence interval (CI) per interquartile range increase in organic solvent exposure

[b]Adjusted for age, gender, race/ethnicity, diabetes, non-occupational noise exposure, smoking, and income

To examine whether organic solvent exposure may differentially affect the occurrence of different types of hearing loss, we ran models testing the association of each of the organic solvents with high-frequency and low-frequency hearing loss, separately (Table 4). As an overall comparison of hearing loss, the odds of hearing loss were higher between organic solvent exposure and high-/low-frequency hearing loss, as compared to audiometrically assessed hearing loss, which was defined as a pure-tone average threshold change greater than or equal to 25 dB in either ear. After controlling for covariates, there was no statistically significant association between any organic solvent and low-frequency hearing loss, but benzene, ethylbenzene, and toluene concentrations remained statistically significantly associated with increased odds of high-frequency hearing loss (benzene adjusted OR 1.43, 95% CI 1.15–1.78; ethylbenzene adjusted OR 1.24, 95% CI 1.02–1.50; and toluene adjusted OR 1.27, 95% CI 1.06–1.52).

To assess if the association of organic solvents and high- and low-frequency hearing loss varied by occupational noise level, we first estimated the association of occupational noise with high-frequency hearing loss. The unadjusted odds of high-frequency hearing loss were statistically significantly higher among those classified as exposed to occupational noise (OR 1.63; 95% CI 1.19–2.24) as compared to those not classified as exposed. Then, we tested occupational noise as both a potential confounder and including an interaction term with the organic solvent exposures. After controlling for covariates, there was not a statistically significant interaction between occupational noise and organic solvent exposure on high-frequency hearing loss (OR 1.16; 95% CI 0.77–1.72). Thus, in the final models we did not adjust for occupational noise.

Discussion

In final adjusted models, we observed no evidence of an association between organic solvent exposure and either hearing loss or tinnitus except in three cases: higher exposures to benzene, ethylbenzene, and toluene were associated with greater odds of high-frequency hearing loss. Similarly,

Table 4 Association between organic solvent exposure and high/low-frequency hearing loss among US adults in NHANES, 1999–2004

Organic solvent (ng/mL)	High-frequency hearing loss adjusted[a] OR[b] (95% CI)	Low-frequency hearing loss adjusted[a] OR[b] (95% CI)
1,4-Dichlorobenzene	0.99 (0.90, 1.09)	0.95 (0.85, 1.07)
Benzene	1.43 (1.15, 1.78)	1.12 (0.89, 1.39)
Ethylbenzene	1.24 (1.02, 1.50)	1.08 (0.89, 1.31)
m-/*p*-Xylene	1.08 (0.93, 1.24)	1.00 (0.86, 1.16)
o-Xylene	1.03 (0.93, 1.13)	1.00 (0.90, 1.11)
Styrene	1.04 (0.94, 1.17)	1.05 (0.94, 1.17)
Toluene	1.27 (1.06, 1.52)	1.03 (0.87, 1.23)

[a]Odds ratio (OR) and confidence interval (CI) per interquartile range increase in organic solvent exposure

[b]Adjusted for age, gender, race/ethnicity, diabetes, non-occupational noise exposure, smoking, and income

occupational studies have shown exposure to a mixture of solvents which included benzene, where exposure was categorized by job title, was positively associated with hearing loss (Fuente et al. 2013b; Rabinowitz et al. 2008). Also, studies have shown exposure to ethylbenzene or toluene has ototoxic effects (Gagnaire and Langlais 2005; Gagnaire et al. 2007a; Waniusiow et al. 2008, 2009).

Our results show the hearing loss frequency range varies with organic solvent exposure. Research has shown exposure to organic solvents can produce cochlear lesions in the inner ear leading to hair cell loss, which is important as hair cells control the frequencies the ear can hear (Campo et al. 2001). Given the potential mechanism for hearing loss at specific frequencies, Morata et al., suggest analyzing high-frequency hearing loss (hearing loss at frequencies of 3, 4, 6 and 8 kHz) when looking at the association between hearing loss and organic solvent exposure, but many researchers use the World Health Organization definition of hearing loss, which is a pure-tone average greater than or equal to 25 dB in either ear at the frequencies of 0.5, 1, 2, and 4 kHz (Morata and Little 2002; World Health Organization 2015). As the frequency of hearing loss can vary by exposure to organic solvents, researchers should consider analyzing the association of organic solvent exposure by the individual octave frequencies of hearing loss as opposed to a general definition of hearing loss.

Previous research demonstrates mixed conclusions on the ototoxicity of organic solvents. Using biomarkers in urine samples, Schaper et al. found a null association between toluene exposure and audiometrically assessed hearing loss of 25 dB or greater (Schaper et al. 2008). Fechter et al. reported a null association between styrene exposure and cochlear function in guinea pigs (Fechter 1993), while human studies also reported a null association between styrene exposure (as measured by job categorization and personal air sampling) in workers and audiometrically assessed hearing thresholds (Hoffmann et al. 2006; Sass-Kortsak et al. 1995), which supports our results. Contrary to our results, *p*-xylene exposure has demonstrated ototoxic reactions in animal studies as well as in certain human studies (Fuente et al. 2013a; Gagnaire et al. 2007b). Likewise, animals given a controlled dose of styrene exposure have shown hearing loss (Yang et al. 2009), while human studies, where styrene exposure was measured by urine and air samples, provide evidence for the association between hearing loss and styrene exposure (Morata et al. 2002, 2011). Additionally, Triebig et al. used blood measurements of styrene and found a statistically significant relationship between styrene exposure and hearing loss (Triebig et al. 2009). Finally, while, to our knowledge, our study is the first epidemiologic study to evaluate, and not finding, an association between blood measurements of organic solvent exposure and tinnitus, a previous case study documented self-reported exposure to toluene or xylene and self-reported tinnitus in the study subject (Gopal 2008). Our results extend limited evidence of the null association between tinnitus and organic solvent exposure but more research is needed.

In view of the differences between our findings and those of previous studies, limitations of our study must also be considered. In summary, possible reasons for our results being contrary to those of previous studies perhaps due to differences in the measurement of solved used to quantify exposure among study participants, differences in hearing loss assessed by audiometry vs. self-report, misclassification of noise exposure, potential residual confounding and sample limitations. Below, we discuss these aspects in more detail.

In our study, exposure to solvents was quantified based on blood measurements, but previous studies that found a statistically significant result used self-reported exposure history (Gopal 2008), urine concentrations, personal air sampling, and job categorization (Fuente et al. 2013a; Hoffmann et al. 2006; Morata et al. 1997; Muijser et al. 1988; Sass-Kortsak et al. 1995). None of these measurement methods may results in accurate predictors of exposure level: self-reported measurements are subject to recall bias; urine concentrations may be subject to high variability related to collection and handling of the samples (Imbriani and Ghittori 2005); personal monitoring might not accurately estimate the internal dose; and, measurements based on job categorization may be too heterogeneous to apply to an individual. Conversely, the use of blood measurements to identify organic solvent exposure has its own limitations. Blood concentrations of organic solvents only characterize recent, not chronic, exposure due to their short half-lives. Thus, the use of a single measure of solvent exposure, like those available from NHANES, results in classical measurement error, which would bias our results toward the null. Future studies should incorporate repeated measures of exposure to reduce bias.

In addition to the differences found in hearing loss based on frequency, there could be important differences in hearing loss assessed by audiometry vs. self-report. In our study, self-reported hearing loss and audiometrically assessed hearing loss followed similar patterns in their associations with organic solvent exposure. These results are in agreement with previous studies (Clark et al. 2014; Sindhusake et al. 2001). Therefore, self-reported data on hearing loss can be used to assess hearing loss, at least for high levels of loss, but audiometry data as well as should be used whenever it is available.

Next, we found no evidence of an interaction between occupational noise and benzene, ethylbenzene, and toluene exposures with high-frequency hearing loss, which is in agreement with Hughes and Hunting (2013) who reported a null association for the interaction between noise and organic solvent exposure on hearing loss (Hughes and

Hunting 2013). On the contrary, a positive interaction on hearing loss between individual organic solvents (including ethylbenzene and toluene but not including benzene) and noise has been demonstrated (Morata et al. 2011; Zhang et al. 2013). Further, epidemiologic studies on workers have also found joint exposure to noise and a mixture of organic solvents, including benzene and styrene, affects hearing loss (Choi and Kim 2014; Unlu et al. 2014). In this study, occupational noise exposure estimation was indirect, based on linking longest held job reported in NHANES to estimates of occupational noise in O*NET. There is a possibility for misclassification of patient due to the crosswalks strategy we used to link the two data sources. Also, the noise estimate was not a direct measure of noise exposure and does not account for inter-individual variability. These reasons could explain the lack of association in reported in this study.

Further, residual confounding may be present in study results as there may be additional confounding factors that were not considered or there may be errors in the classification of study participants with regards to confounding variables. Next, we ran many regressions, and multiple comparisons increase the possibility of detecting a statistically significant association by chance. Nevertheless, detection of statistically significant associations (e.g., among the high-/low-frequency outcomes) by chance seems unlikely because the effect estimates were consistently larger for the high-/low-frequency hearing loss outcomes for each exposure variable as compared to hearing loss assessed by the WHO definition. Additionally, there is potential for information bias in the measurement of tinnitus, noise and other covariates as study participants may incorrectly remember events from the past. Regarding noise levels, we were limited by the availability of data in O*NET, which does not include noise dosimetry data. Additionally, workplaces where solvents may be frequently found (e.g., printing workplaces) might also have high noise levels. If these workers developed hearing problems and changed jobs to a less noisy place that also had less solvent exposure, then our results would be biased towards the null. The extent to this potential bias is not quantifiable because NHANES does not collect occupational history data.

Additional concerns should consider the fact that not all NHANES study participants were included in every component (i.e., laboratory or examination components) of data collection, and subsample weights should be used to reflect the representative proportions of these groups in the population. Unfortunately, the subsamples only partially overlap, which makes the NHANES weighting inappropriate (Centers for Disease Control and Prevention 2013). Although, oversampling of certain study populations may create potential for selection bias, we analyzed associations and did not present proportions so the un-weighted data are likely to be unbiased regarding the accuracy of our results.

Conclusion

We did not find an association between organic solvent exposure and hearing loss (self-reported and audiometrically assessed) or self-reported tinnitus in a large and diverse population with blood measurements of organic solvents. However, we did find evidence of an association between exposure to three organic solvents (i.e., benzene, ethylbenzene, and toluene) and high-frequency hearing loss. Moreover, the effect estimates for high-/low-frequency hearing loss were higher as compared to audiometrically assessed hearing loss defined according to the WHO definition of hearing loss. In view of the limitations of our study, additional research is needed to replicate our findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing financial interests, and all authors certify that their freedom to design, conduct, interpret, and publish this research is not compromised by any controlling sponsor.

Ethical approval The study was approved by The University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects.

Informed consent For this type of study using National Health and Nutrition Examination Survey (NHANES) Public-Use Data files, consent is not required.

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