Exploring the association of organochlorine pesticides exposure and hearing impairment in United States adults

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Hearing loss (HL) is a highly prevalent public health concern. Organochlorine pesticides (OCPs) are widely used environmental pollutants harmful to human health. Studies investigating the effects of OCPs exposure on the auditory system in the general population are rare. To explore the association between OCPs exposure and HL in adults, 366 adults aged 20–69 years who participated in the National Health and Nutrition Examination Survey (NHANES, 2003–2004) were investigated. HL was defined as a pure-tone average (PTA) ≥ 20 dB in the better ear. Multivariate linear and logistic regression analyses were conducted to evaluate the association of four selected serum OCPs with PTAs and the risk of HL. In participants aged < 60 years, hexachlorobenzene (HCB) and dichlorodiphenyldichloroethylene (p, p'-DDE) exposure was positively associated with low- and speech-frequency PTAs, and with low-frequency HL, respectively. Risk of HL increased in the highest tertile compared with the lowest tertile of serum HCB and p, p'-DDE (odds ratio [OR]: 4.38, 95% confidence interval [CI]: 0.97–19.80; OR: 16.66, 95% CI: 2.64–105.09, respectively). In this study of US adults aged < 60 years, HCB and p, p'-DDE exposure was positively associated with HL. HCB and p, p'-DDE may be potential risk factors for HL.

Hearing loss (HL) is a highly prevalent sensory disorder. Globally, it is the third most common cause of disability in humans. It affects people of all ages, causes enormous financial burden, and affects people through the loss of education, communication, and social interaction when HL is left unaddressed. Over 1.5 billion people currently have HL, and this number could grow to 2.5 billion by 20501. To prevent and treat HL, several studies have been conducted to investi
gate its common causes, such as noise exposure, aging, and ototoxic drug use. Concerns have also been raised regarding the role of exposure to environmental pollutants in the development of HL2.

Organochlorine pesticides (OCPs) are persistent organic environmental pollutants that bioaccumulate in food chains. Although some OCPs have been banned or restricted for decades, their extensive usage, long half-lives, and bioaccumulation still affect human health3. Previous studies have shown that OCPs may cause immune dysfunction, endocrine disruption, neurobehavioral and cognitive impairment, and may have chronic effects on reproductive potential, as carcinogens4–8.

Recently, interest has increased regarding the effect of environmental pollutants on the development of hearing impairment2. Although animal studies, experimental studies on humans, and epidemiological surveys have indicated the toxicity of polychlorinated biphenyls (PCBs), another important organochlorine pollutant, on the auditory system, studies investigating the effects of exposure to OCPs on the auditory system are limited9–13. Animal studies have addressed the ototoxicity of organochlorine pesticides dichlorodiphenyldichloroethane (DDT) and hexachlorobenzene (HCB) in rats14–16. A previous study reported that exposure to OCPs, including HCB, β-hexachlorocyclohexane (β-HCH), and p, p'-dichlorodiphenyldichloroethylene (p, p'-DDE, a metabolite of DDT), at environmental concentrations during infancy, may be associated with hearing impairment17. A case–control study indicated that exposure to α-hexachlorocyclohexane (α-HCH), an OCP, might be a potential risk factor for HL18. In this study, we investigated whether there were associations between environmental exposure to OCPs and HL in adults who participated in the National Health and Nutrition Examination Survey.

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(NHANES) 2003–2004. To our knowledge, this is the first cross-sectional study to investigate the effect of OCPs exposure on the auditory system in the general adult population in the US.

Results

Baseline characteristics of study participants. Table 1 shows the baseline characteristics of the participants in this study (n = 366) aged between 20 and 69 years, including 195 females (weighted mean, 40.74 ± 11.77 years) and 171 males (weighted mean, 41.52 ± 14.07 years). The mean ± standard deviation (SD) values of low-, speech-, and high-frequency pure-tone average (PTA) hearing thresholds in the male participants were 8.34 ± 6.76 dB, 11.81 ± 8.33 dB, and 22.84 ± 17.30 dB, respectively. The hearing thresholds were 8.86 ± 7.87 dB, 9.54 ± 7.99 dB, and 15.48 ± 13.90 dB in the female participants, respectively. Overall, HL rates were 14.59% and 8.63% among the male and female participants, respectively. There were statistically significant differences between the male and female participants in speech- and high-frequency PTA, serum cotinine level, and loud noise/music exposure (all P < 0.05).

Comparison of variables among low-, speech- and high-frequency HL groups by univariate analysis. The univariate analysis (Table 2) showed that gender and firearm noise exposure had significant correlations with speech-frequency PTA; gender, race (non-Hispanic Black vs. Mexican American), and serum cotinine level had significant correlations with high-frequency PTA; age, education level, loud noise/music exposure, and hearing loss had significant correlations with low-, speech-, and high-frequency PTA (all P < 0.05).

Multivariate regression analysis: association of OCPs with hearing thresholds and HL. In Supplementary Tables S1 and S2, we estimated the association of the four OCPs with low-, speech-, high-frequency hearing thresholds, and with HL using multivariate linear and logistic regression models, respectively. The
Among individuals aged < 60 years with p, p'-DDE exposure levels in the highest tertile, compared with those in the lowest tertile (OR: 16.66, 95% CI: 2.64–105.09, Pinteraction = 0.0015, Pinteraction = 0.0288); the 95% CI associated with the OR had a wide range. Dieldrin exposure had no statistically significant interactions with age in the prediction of either hearing threshold shifts or HL (Pinteraction > 0.05) (Tables 3 and 4).

Table 2. The univariate analysis of comparison of variables in hearing loss group. SD standard deviation, HL hearing loss, OR odds ratio, CI confidence interval, BMI body mass index, HCB hexachlorobenzene, p, p'-DDE p, p'-dichlorodiphenyldichloroethylene. Significant values are in bold.

| Variables | N (%)/Mean ± SD | Low-frequency HL (N = 31) OR (95% CI) P value | Speech-frequency HL (N = 52) OR (95% CI) P value | High-frequency HL (N = 132) OR (95% CI) P value |
|-----------|-----------------|---------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Age       | 41.74 ± 13.91   | 1.10 (1.06, 1.14) < 0.0001                   | 1.13 (1.09, 1.17) < 0.0001                     | 1.12 (1.09, 1.14) < 0.0001                     |
| Gender (female) | 195 (53.28%)  | 0.93 (0.45, 1.94) 0.8460                      | 0.45 (0.25, 0.83) 0.1042                      | 0.37 (0.24, 0.58) 0.0001                      |

Race/Ethnicity

| Race/Ethnicity | N (%)/Mean ± SD | Low-frequency HL (N = 31) OR (95% CI) P value | Speech-frequency HL (N = 52) OR (95% CI) P value | High-frequency HL (N = 132) OR (95% CI) P value |
|----------------|-----------------|---------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Mexican American | 27 (21.04%)    | 1.0                                          | 1.0                                            | 1.0                                           |
| Non-Hispanic White | 178 (48.63%)  | 1.0                                        | 1.0                                            | 1.0                                           |
| Non-Hispanic Black | 80 (21.86%)   | 0.40 (0.12, 1.35) 0.1392                   | 0.40 (0.15, 1.03) 0.0585                      | 0.48 (0.24, 0.97) 0.0397                      |
| Other races   | 31 (8.47%)      | 0.81 (0.20, 3.21) 0.7639                    | 0.44 (0.12, 1.65) 0.2256                      | 0.68 (0.27, 1.67) 0.3970                      |

Education level

| Education level | N (%)/Mean ± SD | Low-frequency HL (N = 31) OR (95% CI) P value | Speech-frequency HL (N = 52) OR (95% CI) P value | High-frequency HL (N = 132) OR (95% CI) P value |
|-----------------|-----------------|---------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Below high school | 77 (21.04%)   | 1.0                                          | 1.0                                            | 1.0                                           |
| High school     | 90 (24.59%)     | 0.68 (0.28, 1.67) 0.3962                    | 0.60 (0.28, 1.31) 0.2031                      | 0.60 (0.32, 1.11) 0.1031                      |
| Above high school | 199 (54.37%)  | 0.26 (0.10, 0.64) 0.0034                    | 0.37 (0.18, 0.74) 0.0050                      | 0.50 (0.29, 0.86) 0.0117                      |

BMI (kg/m²)

| BMI (kg/m²) | N (%)/Mean ± SD | Low-frequency HL (N = 31) OR (95% CI) P value | Speech-frequency HL (N = 52) OR (95% CI) P value | High-frequency HL (N = 132) OR (95% CI) P value |
|------------|-----------------|---------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Underweight (< 18.5) | 4 (1.09%)    | 1.0                                          | 1.0                                            | 1.0                                           |
| Normal (≥ 18.5, < 25) | 103 (28.14%)  | 0.25 (0.02, 2.72) 0.2563                   | 0.29 (0.03, 3.06) 0.3011                      | 1.18 (0.12, 11.77) 0.8905                     |
| Overweight (≥ 25, < 30) | 124 (33.88%)  | 0.35 (0.03, 3.63) 0.3800                   | 0.58 (0.06, 5.83) 0.6412                      | 2.03 (0.20, 20.05) 0.5456                     |
| Obesity (≥ 30)  | 128 (34.97%)    | 0.23 (0.02, 2.41) 0.2185                   | 0.62 (0.06, 6.27) 0.6876                      | 1.86 (0.19, 18.40) 0.9593                    |

Diabetes

| Diabetes | N (%)/Mean ± SD | Low-frequency HL (N = 31) OR (95% CI) P value | Speech-frequency HL (N = 52) OR (95% CI) P value | High-frequency HL (N = 132) OR (95% CI) P value |
|----------|-----------------|---------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| No       | 181 (50.32%)   | 1.0                                          | 1.0                                            | 1.0                                           |
| Yes      | 121 (33.33%)   | 2.80 (1.02, 7.64) 0.0451                   | 2.27 (0.92, 5.64) 0.0764                      | 1.86 (0.19, 18.40) 0.9593                    |

Hypertension

| Hypertension | N (%)/Mean ± SD | Low-frequency HL (N = 31) OR (95% CI) P value | Speech-frequency HL (N = 52) OR (95% CI) P value | High-frequency HL (N = 132) OR (95% CI) P value |
|--------------|-----------------|---------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| No           | 181 (50.32%)   | 1.0                                          | 1.0                                            | 1.0                                           |
| Yes          | 121 (33.33%)   | 2.27 (0.92, 5.64) 0.0764                   | 1.86 (0.19, 18.40) 0.9593                    | 1.86 (0.19, 18.40) 0.9593                    |

Log HCB (ng/g lipid) 3.89 ± 0.63 1.70 (1.02, 2.82) 0.0401 1.92 (1.24, 2.96) 0.0034 1.51 (1.06, 2.14) 0.2215

Log p, p'-DDE (ng/g lipid) 8.01 ± 1.60 1.65 (1.31, 2.09) < 0.0001 1.58 (1.30, 1.91) < 0.0001 1.41 (1.22, 1.63) < 0.0001

Log nonachlor (ng/g lipid) 3.83 ± 1.31 1.90 (1.39, 2.60) < 0.0001 2.14 (1.63, 2.80) < 0.0001 2.15 (1.74, 2.66) < 0.0001

Log dieldrin (ng/g lipid) 2.63 ± 0.90 1.97 (1.32, 2.95) 0.0009 2.11 (1.50, 2.96) < 0.0001 2.28 (1.72, 3.01) < 0.0001
Aberrant epigenetic and inflammatory mechanisms caused by pesticide exposure are consistent with previous findings. A case–control study reported a positive association between α-HCH exposure and distortion product otoacoustic emissions (DPOAEs), an audiological examination performed at different ages of infants, and by calculating DPOAE amplitudes to serum OCPs reported that exposure to HCB, β-HCH, and p, p'-DDE in infancy may be linked with hearing impairment. Our study is the first cross-sectional study to investigate the effect of OCPs exposure on the auditory system in a sample of the general population of US adults. The results of this study are consistent with previous findings.

Discussion
In a representative sample of US adults aged 20–59 years old, higher serum HCB and p, p’-DDE concentrations were positively correlated with the prevalence of low-frequency HL and with low- and speech-frequency PTA hearing threshold shifts after adjusting for potential confounders including sex, race, education level, BMI, diabetes, hypertension, cotinine, firearm noise exposure and loud noise/music exposure. Our findings suggest that environmental exposure to OCPs may be involved in the development of hearing impairments in adults. It should be noted, however, that the 95% CI associated with the OR (16.66) of HL in the highest tertile relative to the lowest tertile of serum p, p'-DDE had a wide range (2.64–105.09).

Our findings suggest that environmental exposure to OCPs may be involved in the development of hearing impairment21. Although HL caused by PCBs exposure is associated with the induction of hypothyroidism, and exposure to OCPs is associated with adverse thyroid function, no evidence has supported this hypothesis4,6,12,23. In addition, whether exposure to HCB and p, p’-DDE causes otoxicity by affecting the cochlear outer hair cells (OHCs) or other parts of the auditory system (i.e., the organ of Corti, the nerves) remains uncertain: one study showed that DPOAEs (measure for assessing...
Hadjab et al. Contrarily, Sisto et al. found positive associations between HCB and p, p'-DDE exposure and speech-frequency hearing threshold shifts. These results are almost in agreement with those of the study by In our study, HCB and p, p'-DDE exposure was positively associated with low-frequency HL and with low- and middle-frequency hearing loss. Significant values are in bold.

Table 4. Adjusted associations between OCPs and HL stratified by age (N = 366); age < 60 group (N = 308) and age ≥ 60 group (N = 58). Adjusted for gender, race, education level, BMI, diabetes, hypertension, serum cotinine, firearm noise exposure and loud noise/music exposure. OCPs organochlorine pesticides, HCB hexachlorobenzene, p, p'-DDE p, p'-dichlorodiphenyldichloroethylene, BMI body mass index, PTA pure-tone average, HL hearing loss. Significant values are in bold.

OHCs function) was affected by HCB and p, p'-DDE exposure, and another study observed only a slight loss of hair cells (< 1%) in HCB-treated rats, which could also be observed in control animals. In addition, results regarding the range of hearing impairment caused by exposure to OCPs have been inconsistent across studies. In our study, HCB and p, p'-DDE exposure was positively associated with low-frequency HL and with low- and speech-frequency hearing threshold shifts. These results are almost in agreement with those of the study by Hadjab et al. Contrarily, Sisto et al. found positive associations between HCB and p, p'-DDE exposure and DPOAE amplitudes for most of the primary tone frequencies. Zhang et al. observed a relationship between α-HCH exposure and hearing impairment, mainly at mid and high frequencies. Further studies are required to clarify these discrepancies.

This study used a large and representative sample with rigorous quality control over the data collection process and adjusted for critical confounders to establish a relationship between serum OCPs concentrations and hearing impairment. However, this study had several limitations. First, due to the inherent limitation of the cross-sectional design, the temporal sequence of exposures and outcomes cannot be confirmed. Prospective studies are required to definitively define the association between OCPs exposure and hearing function. Second, data of infants, adolescents, and the elderly (≥ 70 years old) were not included in this study due to the lack of participants or the sample size being too small. Moreover, we could not rule out any potential effects of other confounders (e.g., dietary intake, history of ear infection, and congenital hearing impairment) were not addressed in this study. Furthermore, studies on the mechanisms of the effects of HCB and p, p'-DDE exposure on hearing impairment are insufficient. Therefore, functional biological studies (i.e., DPOAE and brainstem auditory evoked potential studies) and prospective population studies are required to investigate the potential mechanisms.

Methods
Study design and population. The NHANES is a nationwide, cross-sectional, representative series of surveys containing health-related information of the US general population. These continuous surveys consist of interviews, physical measurements, and laboratory tests of a selected sample of the US non-institutionalized population. The NHANES project was reviewed and approved by the Research Ethics Review Board of the National Center for Health Statistics, and informed consent was obtained from all participants. Data from the NHANES and related documentation and protocols described in detail are publicly available from the NHANES website (https://www.cdc.gov/nchs/nhanes/Index.htm).
The participants in this report were enrolled from the NHANES cycle 2003–2004, which contains the results of both serum concentrations of OCPs and audiometry examinations of 20–69-year-old adults. Since the analytical detection limits of serum OCPs varied significantly in previous cycles and the sample sizes of recent cycles were quite small, only the data from the 2003–2004 cycle were used in our analysis. Figure 1 shows a flow chart for participant selection in this study. Participants with missing data on hearing threshold levels, otoscopic tests, tympanogram tests, or serum lipid-adjusted concentrations of the selected OCPs were excluded. Individuals with abnormal otoscopic results, poor-quality tympanogram results, or tympanograms with compliance ≤ 0.3 ml were also excluded to avoid analyzing conductive or mixed HL data. Finally, 366 participants were included in this study.

OCPs exposure measurement. Blood serum concentrations of 13 OCPs and metabolites were measured in a random one-third subsample of participants aged 12 years and older using high-resolution gas chromatography/isotope-dilution high-resolution mass spectrometry at the US Centers for Disease Control and Prevention (CDC) National Center for Environmental Health. Four OCPs detected in ≥ 80% of the samples were selected for analysis in our study: HCB, p, p'-DDE, trans-nonachlor, and dieldrin. We used the limit of detection (LOD) divided by the square root of two for any sample below the LOD. In addition, the lipid-adjusted serum concentrations (ng/g lipid) of the four OCPs were used in our study and log-transformed to normalize the skewed distribution before the analysis.

Audiometric measurement. The detailed procedure and protocol of audiometric examination have been described in the NHANES audiometry procedures online manual and previous papers. Briefly, half of the sample of US adults aged 20–69 years underwent an audiometric component test. Trained examiners conducted hearing threshold examinations in a silent and sound-isolating audiometry room. The hearing threshold examination was conducted at seven frequencies from 500 to 8000 Hz using an AD226 audiometer (Interacoustics). In this study, low-frequency HL was defined as PTA calculated by averaging thresholds at 500, 1000, and 2000 Hz ≥ 20 dB HL in the better ear; speech-frequency HL was defined as PTA at 500, 1000, 2000, and 4000 Hz ≥ 20 dB HL in the better ear, which is consistent with the definition used by the World Health Organization; and high-frequency HL was defined as PTA at 4000, 6000, and 8000 Hz ≥ 20 dB HL in the better ear.

Otoscopic examination of both ears was performed using a Welch Allyn otoscope (Model 25,020). Tympanometry was performed using an Earscan Acoustic Impedance tympanometer (Micro Audiometrics) to assess middle ear function. Inference of sensorineural HL was based on the findings of normal otoscopic examinations and good- or adequate-quality results of the tympanogram with compliance > 0.3 ml. Individuals who did not meet the standards were excluded from further analysis.

Covariates. The following variables were considered as potential covariates in the analysis: age and BMI as continuous variables, and sex, race/ethnicity, education level, BMI (categorical), diabetes, hypertension, serum
cotinine level, firearm noise exposure, and noise noise/music exposure as categorical variables. Information on demographic variables, noise exposure, and present medical illnesses, such as diabetes and hypertension, was obtained from self-reported questionnaires. Firearm exposure was defined as “firearm noise exposure outside work for an average of at least once a month for a year”23. Loud noise/music exposure was defined as “exposure to other types of loud noise, such as noise from power tools or loud music, outside work, for an average of at least once a month for a year.” Diabetes was defined by a “yes” or “borderline” answer to the question “other than during pregnancy, ever been told by a doctor or health professional had diabetes or sugar diabetes”30. Hypertension was defined as “ever been told by a doctor or other health professional had hypertension, also called high blood pressure”30. BMI was obtained through physical examination. Serum cotinine level, a marker for both active and passive tobacco exposure, was tested by an isotope dilution-high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry31.

Statistical analysis. Weighted statistical differences in demographic and potential hearing-related variables between individuals grouped by sex were evaluated, with categorical data presented as percentages and continuous data as mean ± SD. The $P$ values of the continuous and categorical data were estimated using a weighted linear regression model and weighted chi-square test, respectively. We distributed the log-transformed lipid-adjusted OCP levels into tertiles before conducting univariate analysis to estimate potential variables. Multivariate linear regression analysis was used to determine regression coefficients ($\beta$) and 95% CIs between the four OCPs and hearing threshold shifts, and multivariate logistic regression analysis was used to estimate ORs and 95% CIs between the four OCPs and HL, adjusting for age, gender, race/ethnicity, education level, BMI (categorical), diabetes, hypertension, serum cotinine level, firearm noise exposure, and loud noise/music exposure, instead of using sample weights. This adjustment is considered a good compromise between efficiency and bias32,33. We evaluated the influence of the interactions between the OCPs and age on HL. Stratified multivariate linear and logistic regression analyses according to age ($< 60$ vs. $\geq 60$ years) were performed. The association between trans-nonachlor exposure and HL was not estimated in the multivariate linear and logistic regression analyses stratified by age because the number of participants aged $\geq 60$ years in the category of low trans-nonachlor exposure tertile was quite small, and only two individuals were included. Statistical analysis was conducted using the statistical programming language R 3.6.1 and EmpowerStats software (X&Y Solutions, Inc.). A $P$-value $< 0.05$ was considered statistically.

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L.L. and X.T. contributed to the conceptualization. L.L. performed formal analysis and interpretation of data, wrote original draft. X.T. revised the manuscript. All authors reviewed and approved the final manuscript as submitted.

**Competing interests**
The authors declare no competing interests.

**Additional information**

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