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# Use of the kurtosis statistic in an evaluation of the effects of noise and solvent exposures on the hearing thresholds of workers: An exploratory study

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The aim of this exploratory study was to examine whether the kurtosis metric can contribute to investigations of the effects of combined exposure to noise and solvents on human hearing thresholds. Twenty factory workers exposed to noise and solvents along with 20 workers of similar age exposed only to noise in eastern China were investigated using pure-tone audiometry (1000–8000 Hz). Exposure histories and shift-long noise recording files were obtained for each participant. The data were used in the calculation of the cumulative noise exposure (CNE) and CNE adjusted by the kurtosis metric for each participant. Passive samplers were used to measure solvent concentrations for each worker exposed to solvents over the full work shift. Results showed an interaction between noise exposure and solvents for the hearing threshold at 6000 Hz. This effect was observed only when the CNE level was adjusted by the kurtosis metric.

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## I. INTRODUCTION

In today's complex industrial environments, noise and chemicals, such as solvents, are found in many workplaces, and are part of the daily life of numerous workers. Studies conducted with experimental animals provide robust evidence that solvents, such as toluene, styrene, xylene, and ethyl benzene, can affect the auditory function through their toxic action on the organ of Corti, auditory pathways, as well as on the middle-ear reflex (Venet *et al.*, 2011; Wathier *et al.*, 2016). In addition, aromatic solvents can interact synergistically with noise. Previous studies, also on experimental animals, elucidated mechanisms and dose-effect relationships between agents and effects on the auditory function (for a review, see Johnson and Morata, 2010, and Campo *et al.*, 2013). Human studies have shown that workers exposed to solvents and noise exhibit a higher prevalence of hearing loss in comparison to noise-exposed or non-exposed control subjects, as well as an association between solvent exposure, audiometric thresholds, and central auditory dysfunction (for a review, see Johnson and Morata, 2010; Rawool, 2016).

Noise exposures often vary in the temporal pattern in many work environments. Jobs involving maintenance work, metalwork, and power tools, such as impact wrenches and nail guns, provide examples of complex noise environments. Typically, as the temporal distribution of these noise

environments is not normal or Gaussian (G), they may be described as “complex non-Gaussian (non-G)” noise (Hamernik *et al.*, 2003). Non-G noise is very common in factories where it is comprised of a background G noise along with embedded high-level transients (impacts or noise bursts). Evidence that noise exposures, including impulse or impact noise, produce greater traumatic effects to the peripheral auditory receptor than the expected damage estimated by the equal-energy hypothesis is available from studies with both animals (Lei *et al.*, 1994; Hamernik and Qiu, 2001) and humans (Thiery and Meyer-Bisch, 1988). Thus, it is evident that an energy metric alone is not sufficient to characterize a non-G noise for the assessment of the effects of noise exposure. Results from animal experiments and human epidemiological studies (e.g., Hamernik *et al.*, 2003; Zhao *et al.*, 2010) have shown that the kurtosis of the amplitude distribution, a statistical metric that is sensitive to the peak and temporal characteristics of a noise, could be a very good descriptor of the resulting auditory damage induced by complex noise exposures. The statistical metric kurtosis ( $\beta$ ), an index of the extent to which the distribution of a variable deviates from the G, is defined as the ratio of the fourth-order central moment to the squared second-order central moment of a distribution. The kurtosis ( $\beta$ ) can be computed on the amplitude distribution of the temporal waveform of the noise given to the subject or by filtering the waveform, a frequency specific kurtosis [ $\beta(f)$ ] can be computed on the resultant time-domain signal (Qiu *et al.*, 2013).

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More recently, the effects of solvent exposure combined with exposure to two different types of noise with the same spectral composition were compared in experimental studies. The first study with styrene was a 6-h continuous noise of 86.2 dB sound pressure level (SPL) (LEX, 8 h = 85 dB SPL) and complex noise consisting of series of sound bursts at 112 dB (LEX, 8 h = 80 dB SPL). The latter combination (styrene and impulse noise) was more harmful to the rat cochlea (Campo *et al.*, 2014). Similar results were found for carbon disulfide (Carreres Pons *et al.*, 2017). The mechanism behind this specific interaction involves an effect of solvents on acoustic reflexes. The middle-ear acoustic reflex (MER) is driven by a cholinergic efferent system and *in vivo* studies have shown that it can be affected by solvents (Maguin *et al.*, 2009; Venet *et al.*, 2011). A dysfunction of this reflex would increase the risk for hearing loss by allowing higher acoustic energy levels (at least 5 dB) to penetrate the inner ear (Campo *et al.*, 2014; Carreres Pons *et al.*, 2017). Thus, the combined exposure to noise and solvents may be particularly harmful to the human auditory system in the presence of non-G noise.

In the current exploratory study, we examined the effects of combined exposure to solvents and complex noise on hearing thresholds of workers from eastern China using a kurtosis metric, which takes into consideration the temporal structure of the noise. The ultimate goal was to investigate whether the kurtosis metric can contribute to the study of combined effects.

## II. METHODS

### A. Study population

Initially, an occupational hygienist at the Zhejiang Provincial Center for Disease Control and Prevention of China administered a questionnaire to each worker in order to collect information regarding occupational history (type of factory, worksite, job description, length of employment, duration of daily noise exposure, and history of use of hearing protectors). Also, through this questionnaire a medical history for each worker was obtained. The characteristics of the study population ( $n = 40$ ) regarding their age, tenure, and exposures to noise and solvents are shown in Table I.

Workers exposed to solvents and noise ( $n = 20$ ) were volunteers from two furniture-making factories located in Wenzhou, China. They were exposed to a mixture of solvents, including acetone, ethyl acetate, methyl ethyl ketone (MEK), benzene, toluene, butyl acetate, ethyl benzene, xylene, and styrene. These workers mainly performed duties that involved painting. Noise-exposed workers ( $n = 20$ ) were selected from five manufacturing factories from Hangzhou, China. These workers were mainly involved in assembly and tandem rolling duties. For both groups of workers, noise exposure levels varied throughout their work shift. The same was true for solvent exposure levels (for workers exposed to both agents). Workers from all factories mentioned above had not been offered hearing protection for most of their working history. Painting workers wore half mask respirators (Hangzhou Lantian Labor Protective Equipment Factory, model 2102, Hangzhou, P.R. China) only when they painted the furniture. Similarly to hearing protection, the effectiveness of half mask respirators is dependent on the adequacy of their use. This

TABLE I. Characterization of the study population ( $n = 40$ ). Mean values, range, and standard deviation (SD; within parenthesis) for the variables of age, tenure, current time-weighted noise and solvent exposures, and estimated cumulative noise exposures (CNEs). (NA denotes “not applicable.”)

Variable	Noise ( $n = 20$ )	Noise and solvents ( $n = 20$ )
Age (years)	35.8 (27–49, SD 6.6)	36.7 (25–47, SD 6.7)
Gender	17 males, 3 females	17 males, 3 females
Tenure (years)	7.1 (3–16, SD 3.3)	5.9 (2–16, SD 4.2)
Exposures		
$L_{Aeq}$ (in dBA)	87 (81–93.8, SD 3.7)	86.6 (82–91.5, SD 3)
Kurtosis	30 (5.2–214, SD 44)	26.7 (7–102, SD 22)
CNE (dBA by year)	95 (88–103.8)	94.4 (88–103.6)
Solvent mixture dose (%)	NA	6%–93%
Acetone (ppm)	NA	TWA < 0.1–2.4
Ethyl acetate (ppm)	NA	TWA < 0.07–1.85
Methyl ethyl ketone (MEK) (ppm)	NA	TWA < 0.04–0.15
Benzene (ppm)	NA	TWA < 0.03
Toluene (ppm)	NA	TWA 0.07–12.4
Butyl acetate (ppm)	NA	TWA 0.94–6.9
Xylenes (ppm)	NA	TWA < 0.06–9.8
Styrene (ppm)	NA	(<0.03–8.2)

information was not available during data collection. The proper use of the masks reduces the amount of solvents into the body through the respiratory system. Using the masks only during painting activities does not fully protect workers against solvent exposure as in the same environment other workers may still be painting and, thus, environmental solvent levels increase, or residual exposure might occur following the completion of the task.

Participants reported no history of ear disease, treatment with ototoxic drugs, hypertension, diabetes, or head injury. Their job history showed that this is a very stable population in terms of remaining in one company for a long tenure. All participants provided signed consent forms approved by the Ethics Committee of Zhejiang Provincial Centers for Disease Control and Prevention of China prior to testing, and research was conducted in compliance with the principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2013).

### B. Audiological assessment

The audiometric testing was conducted in a double-walled, sound-treated room. An Interacoustics AC33 clinical audiometer with TDH-39 P headphones (Middelfart, Denmark) was used for pure-tone audiometry (PTA). Tympanometry was carried out with an Interacoustics AZ7 middle-ear analyzer. Air-conduction pure-tone thresholds were tested from 1000 to 8000 Hz and from 1000 to 4000 Hz for bone conduction. Workers were tested prior to the commencement of their work shift in the early morning.

### C. Noise exposure assessment

Shift-long noise recording files were obtained for each study participant using a digital noise dosimeter/recorder

(ASV5910-R, Hangzhou Aihua Instruments Co. Ltd., Hangzhou, P.R. China) operating continuously at a 48 kHz sampling rate. The recorder was equipped with a 1/4-inch microphone, having a flat frequency response ranging from 10 Hz to 20 kHz, and a measurement range of 40–141 dBA. The device was easily worn on the worker’s shoulder just like a typical noise dosimeter. Immediately after recording the noise exposure, the data were transferred from the recorder to a hard disk drive for subsequent analyses. The recorder was calibrated before and after each sampling period using a sound level calibrator (Hangzhou Aihua Instruments, AWA6221B) according to the manufacturer’s instructions.

The sample kurtosis of the recorded noise signal was computed for consecutive 40-s time windows over the full shift using MATLAB software (Natick, MA). For a sample of  $n$  values the sample kurtosis is calculated as

$$\beta = \frac{\frac{1}{n} \sum_{i=1}^n (x_i - \bar{x})^4}{\left( \frac{1}{n} \sum_{i=1}^n (x_i - \bar{x})^2 \right)^2}, \quad (1)$$

where  $x_i$  is the  $i$ th value and  $\bar{x}$  is the sample mean.

Kurtosis is dependent on the length of the window over which the calculation is made and the sampling rate at which the noise waveform is recorded. A window of 40 s was chosen as a compromise that allowed for computational efficiency and reflected the dynamic features of complex noise. The selection of 40-s time window was based on previous animal data with a sampling rate of 48 kHz (Hamernik *et al.*, 2003; Qiu *et al.*, 2007; Qiu *et al.*, 2013), which was found to be sufficient for establishing an acceptable measure of the kurtosis. The mean kurtosis of these 40-s windows was calculated and used as the kurtosis value for the entire shift. Both energy and duration of noise exposure should be taken into account in the evaluation of noise-induced hearing loss to an individual worker. Thus, a composite noise exposure index, the cumulative noise exposure (CNE) in dBA · year, was used to quantify the noise exposure for each subject (Zhao *et al.*, 2010). The CNE is defined as

$$\text{CNE} = L_{\text{Aeq},8\text{h}} + 10 \log T, \quad (2)$$

where  $L_{\text{Aeq},8\text{h}}$  is the equivalent continuous  $A$ -weighted noise exposure level normalized to an 8-h working day, in decibels, occurring over the time interval  $T$  in years. To evaluate the effects of non-G noise, a kurtosis-adjusted CNE is calculated based on Eq. (2). The new term, kurtosis-adjusted CNE or  $\text{CNE}(\beta)$  in dBA · year is defined as (Zhao *et al.*, 2010)

$$\begin{aligned} \text{CNE}(\beta) &= \text{CNE}_{\text{kurtosis-adjusted}} \\ &= L_{\text{Aeq},8\text{h}} + \frac{\ln(\beta) + 1.9}{\log(2)} \log(T). \end{aligned} \quad (3)$$

This form was chosen for calculating the kurtosis-adjusted CNE because G noise has a kurtosis of  $\beta = 3$ , and the term  $[(\ln(\beta) + 1.9)/\log(2)]$  becomes equal to 10. Thus, for G noise, the kurtosis-adjusted CNE equals the unadjusted

CNE. When the noise is non-G where  $\beta > 3$ , the term  $[(\ln(\beta) + 1.9)/\log(2)]$  becomes larger than 10. It is equivalent to prolong the exposure duration at the fixed  $L_{\text{Aeq},8\text{h}}$ . It can be seen from Eq. (3) that for a fixed  $L_{\text{Aeq},8\text{h}}$ , the kurtosis-adjusted CNE will be larger for non-G noise ( $\beta > 3$ ) than for G noise ( $\beta = 3$ ). In fact, using Eq. (3), the kurtosis metric  $\beta$  logarithmically “tunes” the standard CNE. The introduction of the kurtosis variable into the temporal component of the CNE calculation allows us to quantify the deviation of the non-G noise environment from the G noise environment.

## D. Solvent exposure assessment

Passive samplers (SKC 575-001, SKC Inc., Eighty Four, PA) were used to measure solvent concentrations for each worker exposed to solvents over the full work shift. To determine the level of exposure, a personal, full-shift, time-weighted average (TWA) exposure evaluation was conducted for all the workers. The mixture of solvents included acetone, ethyl acetate, MEK, benzene, toluene, butyl acetate, ethyl benzene, xylene and styrene, and was expressed as a TWA in ppm for each individual component. To evaluate the exposure to the solvent mixture we used the web tool *Mixie* created by the University of Montreal and the Institut de Recherche Robert-Sauvé en Santé et en Sécurité du Travail (IRSST; Vyskocil and Droled, 2010; Vyskocil *et al.*, 2007). It is aimed at assessing the risks associated with exposure to a mixture of airborne chemical substances in the workplace. Toxicological effects are considered additive and the multiple exposure index [ $R_m$ , see Eq. (4) below] is used for assessing the risk encountered by people exposed to several substances present in the workplace,

$$R_m = \sum_{i=1}^n \frac{\text{concentration of substance}_i}{\text{substance}_i \text{ occupational exposure limit (OEL)}}. \quad (4)$$

The sum of the fractions of measured individual exposure concentrations and their time-weighted average exposure value (TWA EV) for each substance results in a percentage of the recommended dose of the mixture. A percentage of 100 indicated that exposures are at their recommended exposure limit (according to Canadian OEL).

## E. Statistical analyses

Hearing thresholds [dB hearing level (HL)] at each single test frequency from 1000 to 8000 Hz were used in the statistical analyses to examine differences in hearing thresholds between workers exposed to noise only and workers exposed to noise and solvents. Considering that workers between both groups were matched by age, gender, noise exposure level and length of employment, the models were not adjusted by these variables, as in this case it could have affected the precision of the estimates. Additionally, a possible association between the hearing threshold at individual frequencies from 1000 to 8000 Hz and CNE, as well as  $\text{CNE}(\beta)$ , was explored in the whole group of subjects ( $n = 40$ ). The explained variance was estimated for each model.

For all the models created, the assumption of homoscedasticity was evaluated through the Breusch–Pagan (Breusch

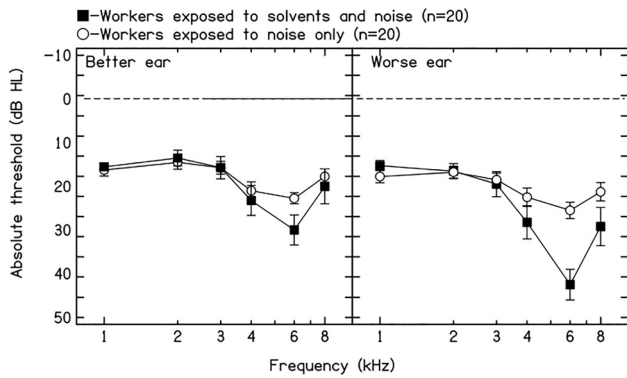


FIG. 1. Mean pure-tone thresholds and standard errors for the better and worse ears for both groups of workers (exposed to noise or exposed to noise and solvents).

and Pagan, 1979) and Cook–Weisberg (Cook, 1983) tests. This assumption was not found for the majority of the models and, thus, an estimator of robust variance (Huber sandwich estimator) was used (Huber and Ronchetti, 2009; White, 1980). Due to the small sample size, the standard errors were estimated through bootstrapping (10 000 replications). The 95% confidence intervals were obtained through a bias-corrected and -accelerated (BCa) method (Efron, 1987), which has shown the least capacity for a coverage error.

Then, interaction terms between CNE and  $CNE(\beta)$  and exposure group (noise only, noise and solvents) were created and included in new models. The predictions from the models were separated by exposure group and then graphically represented. The change in slope for the relationship between CNE and  $CNE(\beta)$  and hearing thresholds in each exposure group, as well as the significance of the interaction term, were the most important contributing aspects in concluding whether there was a multiplying effect in the interaction. Finally, for the group of workers exposed to solvents and noise ( $n = 20$ ) correlations between hearing thresholds at each test frequency (1000–8000 Hz) and (a) dose of the exposure to solvents and (b) dose of the exposure to solvents multiplied by CNE and  $CNE(\beta)$  were computed. The statistical program STATA version 13 was used (StataCorp, 2013).

### III. RESULTS

Figure 1 displays hearing thresholds for the better and worse ears for both groups of workers. Five workers exposed to solvents and noise exhibited significant threshold differences ( $>10$  dB) between the right and left ears. Considering that these differences are difficult to explain solely on their work exposures, we took the conservative approach to focus the rest of the data analyses on the results of their better ear. Workers exposed to solvents and noise exhibited a significantly worse hearing threshold for the better ear than workers exposed only to noise at 6000 Hz (see Table II).

A statistically significant association between CNE and hearing thresholds (for the better ear) at 6000 and 8000 Hz was found. The variance explained by these relationships was 13.3 and 8.9, respectively. When the CNE was adjusted by kurtosis, the variance explained by the combined metrics

TABLE III. Association between cumulative noise exposure (adjusted and not adjusted by kurtosis) and the hearing threshold (in dB HL) for the better ear in the range from 1000 to 8000 Hz ( $n = 40$ ;  $* p < 0.05$ ).

Frequency (better ear)	Robust estimation of variance. Differences in hearing thresholds (95% CI)	Bootstrapping (BCa method; 95% CI)	Explained variance
CNE			
1000 Hz	0.24 (−0.12–0.59)	−0.11–0.60	3.66
2000 Hz	0.24 (−0.39–0.86)	−0.33–0.86	1.72
3000 Hz	0.46 (−0.33–1.24)	−0.35–1.15	4.20
4000 Hz	0.76 (−0.43–1.96)	−0.47–1.81	6.38
6000 Hz	1.06 (0.17–1.96)*	0.19–1.95*	13.36
8000 Hz	0.98 (−0.03–2.00)	0.05–2.05*	8.95
$CNE(\beta)$			
1000 Hz	0.16 (−0.07–0.39)	−0.08–0.39	3.37
2000 Hz	0.24 (−0.19–0.66)	−0.14–0.69	3.55
3000 Hz	0.40 (−0.13–0.93)	−0.14–0.88	6.60
4000 Hz	0.72 (−0.08–1.52)	−0.07–1.48	11.68
6000 Hz	0.80 (0.14–1.45)*	0.19–1.45*	15.49
8000 Hz	0.82 (0.12–1.52)*	0.22–1.59*	12.82

$CNE(\beta)$  and hearing thresholds at 6000 and 8000 Hz increased to 15.49 and 12.82, respectively (see Table III).

Since CNE and  $CNE(\beta)$  were significantly associated with hearing thresholds at 6000 and 8000 Hz, a further analysis was carried with the aim to determine a possible interaction between CNE and solvent exposure. The interaction term between CNE and exposure group on hearing thresholds (1000–8000 Hz) was not statistically significant. However, the interaction term between  $CNE(\beta)$  and exposure group showed a statistically significant effect for 6000 Hz (Beta = 1.10; 95% CI: 0.11–2.09;  $p = 0.03$ ). Thus, the predictions for this model were separately estimated for each group and then graphically represented [see Figs. 2(c) and 2(d)]. As a comparison, the model for 4000 Hz is also included [see Figs. 2(a) and 2(b)].

Finally, a further stratified analysis with workers exposed to solvents and noise ( $n = 20$ ) was carried out to determine a possible dose–response relationship between noise/solvent exposure and hearing thresholds. Pearson correlation matrices were created between hearing thresholds at each test frequency for the better ear (1000–8000 Hz) and (1) the dose of the exposure to solvents (Mixie results; see Table I), (2) an interaction term between dose of exposure to

TABLE II. Differences in hearing thresholds (in dB HL) for the better ear between workers exposed to noise only and workers exposed to noise and solvents. (Reference group: workers exposed to noise only.  $*p < 0.05$ ). CI denotes confidence interval.

Frequency (better ear)	Robust estimation of the variance. Differences in hearing thresholds (95% CI)	Bootstrapping (BCa method; 95% CI)	Explained variance
1000 Hz	−0.75 (−4.10–2.60)	−3.9–2.63	0.50
2000 Hz	−1.00 (−5.87–3.87)	−5.42–4.0	0.50
3000 Hz	0.00 (−5.99–5.99)	−5.13–6.25	0.00
4000 Hz	2.25 (−5.86–10.36)	−5.0–10.60	0.82
6000 Hz	7.25 (−0.22–14.72)	0.56–15.07*	9.22
8000 Hz	2.25 (−6.58–11.08)	−4.82–12.60	0.70

solvents and CNE, and (3) an interaction term between dose of exposure to solvents and CNE( $\beta$ ). Both interaction terms implied a multiplication between both factors. No significant correlations ( $p > 0.05$ ) between hearing thresholds and the three factors mentioned above were observed.

#### IV. DISCUSSION

In this study, a kurtosis metric was used to evaluate the effects of noise and solvent exposures on the hearing

thresholds of industrial workers. The initial comparison of the bilateral hearing thresholds showed a large between-ear threshold differences. This raises the question on whether non-occupational exposures (such as fireworks, commonly used in China) might explain the unilateral losses. However, all five workers presenting with asymmetrical losses were exposed to solvents and noise. Previous reports have found that ototoxins, such as opioids, may induce asymmetrical hearing loss (e.g., [Rawool and Dluhy, 2011](#)). Thus, while it may be hypothesized that industrial solvents may induce a

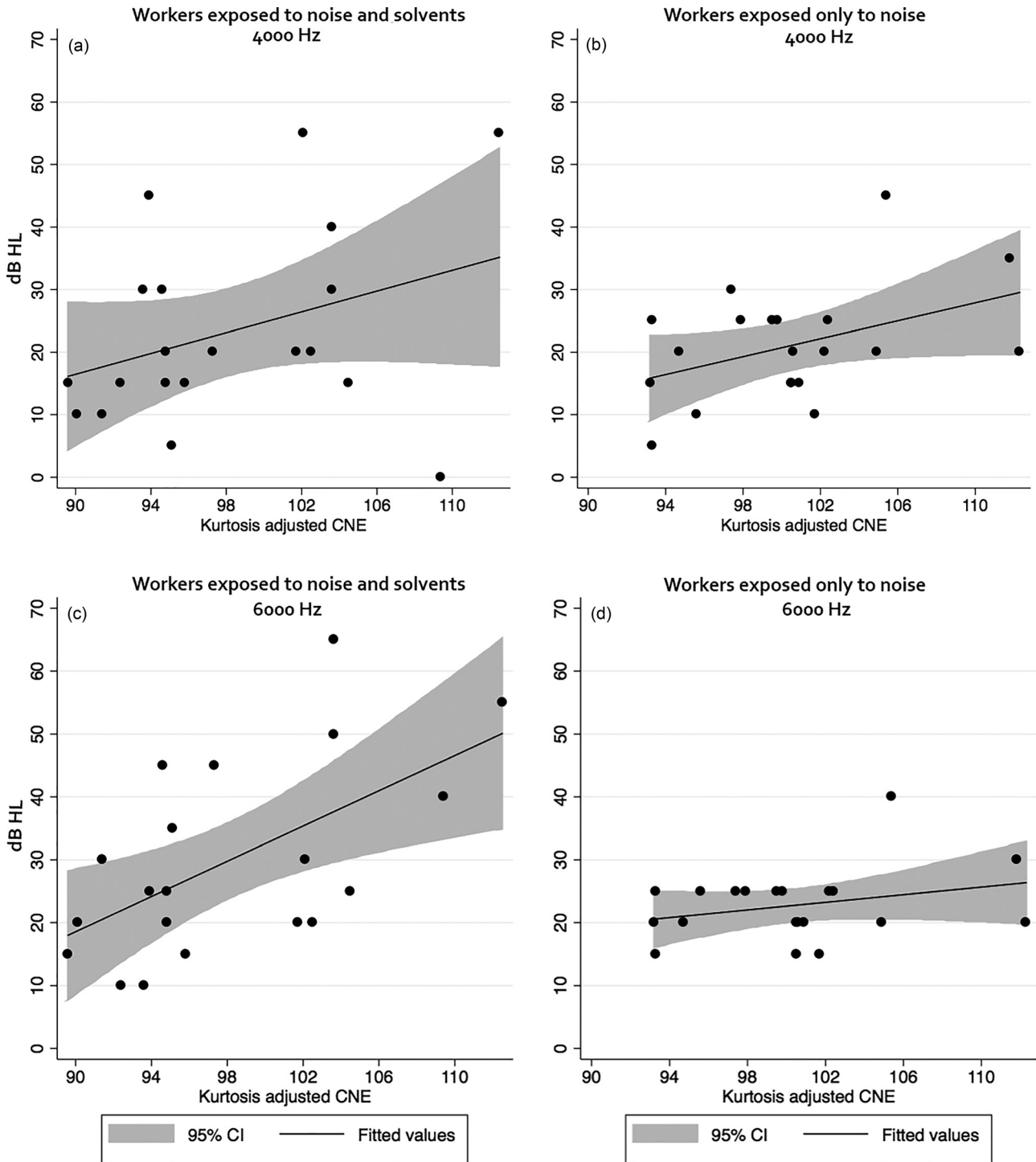


FIG. 2. Predicted hearing thresholds (in dB HL) for 4000 Hz (a),(b) and 6000 Hz (c),(d) for workers exposed to noise and solvents (a),(c) and workers exposed only to noise (b),(d).

similar effect, no evidence supporting this hypothesis is currently available. So, while work exposures might have contributed to the losses in both ears, we decided to complete the analysis only considering the better ear.

Results showed that workers exposed to non-G noise and solvents presented a significantly worse hearing threshold at 6000 Hz for the better ear than workers exposed only to non-G noise. Further analyses showed an interaction effect between noise and solvent exposure at 6000 Hz but only when CNE was adjusted by kurtosis. Estimations for hearing thresholds were obtained for each group separately (noise only/noise and solvents) and graphically represented (Fig. 2). The estimations should run parallel for both groups [as observed for 4000 Hz, Figs. 2(a) and 2(b)], but this is lost for 6000 Hz [Figs. 2(c) and 2(d)], thereby serving as an indicator of interaction. As it can be observed in Figs. 2(c) and 2(d), the slope for predicted hearing thresholds at 6000 Hz is much more pronounced among workers exposed to noise and solvents than workers only exposed to noise. The change in slope for the relationship between CNE level adjusted by kurtosis and hearing thresholds in each exposure group, as well as the significance of the interaction term, were the most important contributing findings in concluding there was an effect modification from the solvent exposure. The change in slope, in addition to the significant interaction term observed, suggest that an interaction between noise and solvent exposure did occur at 6000 Hz. To the best of our knowledge, this is the first study that shows the temporal parameter of noise exposure and the modification of their auditory effects by solvents in humans. We hypothesize that the interaction between noise and solvent exposure was only observed at 6000 Hz and when noise exposure was adjusted by kurtosis because previous studies have shown that 6000 Hz is the most affected frequency by impulse noise (e.g., Mäntysalo and Vuori, 1984; Thiery and Meyer-Bisch, 1988). For example, Thiery and Meyer-Bisch (1988) reported that workers exposed to impulse noise presented with worse hearing thresholds at 6000 Hz than workers exposed to a continuous noise at 95 dBA ( $L_{Aeq,8h}$ ). In addition, in this study, workers exposed to noise and solvents reported a mean exposure history of six years, which is in agreement with previous reports suggesting that up to around six years, 6000 Hz is the most affected frequency by exposure to impulse noise (Mäntysalo and Vuori, 1984). Thus, in this study we observed that solvent exposure has exacerbated the main auditory effect induced by impulse noise. The results should, however, be taken with caution due to the limited number of workers investigated. Noise levels were obtained for a typical working day. However, information about past working conditions was not available and, thus, the noise exposure data may not fully represent worker's real exposure levels during their entire working life. Similarly, regarding solvent exposure it is possible that workers were exposed to higher concentrations of solvents in the past where less strict regulations were in place.

Regarding a possible dose-response relationship between hearing thresholds and noise/solvent exposure, no such an effect was found for either of the factors considered [i.e., dose of solvent exposure alone and combined with

CNE and CNE( $\beta$ )]. One explanation for the absence of a dose-response relationship may be the fact that longitudinal data regarding solvent exposure are hard to obtain, similar to noise exposures. Thus, current doses of solvent exposure may not be representative of workers' dose of exposure during their entire working life. Another possible explanation is that a linear relationship between solvent exposure alone or combined with noise and hearing thresholds does not occur in humans, as it does in experimental animals. Moreover, hearing outcomes are linked to several endogenous and exogenous factors, and the variability within and across populations makes such determinations very challenging to measure. So far the majority of previous studies in humans have not been able to find a dose-response relationship between solvent exposure dose and hearing thresholds (e.g., Morata *et al.*, 2011; Sliwinska-Kowalska *et al.*, 2003). As previously mentioned, the evaluation of chemical exposure in this current study was very limited and the exposure levels varied widely. The current solvent exposures of the studied group varied from very low levels during most of their work shift, to a few periods of high concentrations. Research conducted to date does not offer answers on whether the solvent effects observed in humans are caused by long-term exposure to low-level background solvent levels or if they are triggered by few peaks of high solvent concentration. Are the peaks of solvent exposure more damaging than continuous low levels of the same 8-h TWA, as it has been shown to happen with noise? Perhaps this question can be answered in an investigation with a larger sample size and detailed chemical exposure assessments (e.g., longitudinal data).

Regarding the interaction between noise and solvents, Campo *et al.* (2014) observed that the temporal structure of noise exposure (continuous versus impulsive) modified the ototoxicity of styrene in experimental animals. A moderate concentration of styrene potentiated the cochlear damage caused by impulse noise, but it reduced the damage caused by continuous noise. The explanation offered for this paradox was that the natural protective mechanisms of the MER is modified by solvent exposure by lowering the threshold that triggers it. In addition, the MER amplitude is modified by solvent exposure. While an exposure to continuous noise can be attenuated by the MER, the same does not hold true for exposures to impulse noise, as the acoustic energy of this type of noise is dissipated into the cochlea before the MER is triggered (Borg *et al.*, 1984). The protective role of the MER therefore can become insignificant for impulse noises, resulting in a difference between noises even when the  $L_{Aeq,8h}$  are similar. This argument could also explain why co-exposure to noise and solvents can modify the effects of noise on individuals' hearing. Similarly, this may explain why in this study we have found an interaction between noise and solvent exposure only when noise exposure levels were adjusted by kurtosis. From a preventive point of view, (a) the use of the equal energy principle over an 8-h workday ( $L_{Aeq}$ ) is not enough to estimate risk of hearing loss in complex noise environments, and (b) co-exposures to ototoxic agents, if present, should be taken into account.

This small-scale study aimed to investigate whether the kurtosis metric is applicable for predicting risk from

combined exposures to noise and solvents. Our findings suggest that it is the case and that the potential interaction of solvents and impulse noise merits further research. Ideally, one would measure exposure ranges and peaks levels for both noise and solvent exposure. Audiological tests that evaluate central auditory functions should also be considered, given the limitations of the information provided by PTA.

In conclusion, this study provides evidence that using a metric that incorporates the impulsiveness of noise combined with solvent exposure can allow the detection of their effects on hearing threshold.

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Borg, E., Counter, S. A., and Röster, G. (1984). "Theories of middle-ear muscle functions," in *The Acoustic Reflex: Basic Principles and Clinical Applications*, edited by S. Silman (Academic, Orlando, FL), pp. 63–101.

Breusch, T. S., and Pagan, A. R. (1979). "A simple test for heteroscedasticity and random coefficient variation," *Econometrica* **47**, 1287–1294.

Campo, P., Morata, T. C., and Hong, O. (2013). "Chemical exposure and hearing loss," *Dis. Mon.* **59**(4), 119–138.

Campo, P., Venet, T., Thomas, A., Cour, C., Brochard, C., and Cosnier, F. (2014). "Neuropharmacological and cochleotoxic effects of styrene. Consequences on noise exposures," *Neurotoxicol. Teratol.* **44**, 113–120.

Carreres Pons, M., Chalansonnet, M., Venet, T., Thomas, A., Nunge, H., Merlen, L., Cosnier, F., Llorens, J., and Campo, P. (2017). "Carbon disulfide potentiates the effects of impulse noise on the organ of Corti," *Neurotoxicology* **59**, 79–87.

Cook, R. D., and Weisberg, S. (1983). "Diagnostics for heteroscedasticity in regression," *Biometrika* **70**, 1–10.

Efron, B. (1987). "Better bootstrap confidence intervals," *J. Am. Stat. Assoc.* **82**(397), 171–185.

Hamernik, R. P., and Qiu, W. (2001). "Energy-independent factors influencing noise-induced hearing loss in the chinchilla model," *J. Acoust. Soc. Am.* **110**(6), 3163–3168.

Hamernik, R. R., Qiu, W., and Davis, B. (2003). "The effects of the amplitude distribution of equal energy exposures on noise-induced hearing loss: The kurtosis metric," *J. Acoust. Soc. Am.* **114**(1), 386–395.

Huber, P. J., and Ronchetti, E. M. (2009). *Robust Statistics*, 2nd ed. (Wiley, Hoboken, NJ).

Johnson, A. C., and Morata, T. C. (2010). "Occupational exposure to chemicals and hearing impairment. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals," *Arbete o Hälsa*, Vol. 44(4), Nordic Expert Group, Gothenburg, pp. 1–177, available at <https://gupea.ub.gu.se/handle/2077/23240> (Last viewed 10 July 2017).

Lei, S. F., Ahroon, W. A., and Hamernik, R. P. (1994). "The application of frequency and time domain kurtosis to the assessment of hazardous noise exposures," *J. Acoust. Soc. Am.* **96**(3), 1435–1444.

Maguin, K., Campo, P., and Parietti-Winkler, C. (2009). "Toluene can perturb the neuronal voltage-dependent Ca<sup>2+</sup> channels involved in the middle-ear reflex," *Toxicol. Sci.* **107**, 473–481.

Mäntyselä, S., and Vuori, J. (1984). "Effects of impulse noise and continuous steady state noise on hearing," *Br. J. Ind. Med.* **41**, 122–132.

Morata, T. C., Sliwiska-Kowalska, M., Johnson, A. C., Starck, J., Pawlas, K., Zamysłowska-Szmytko, E., Nylén, P., Toppila, E., Krieg, E., Pawlas, N., and Prasher, D. (2011). "A multicenter study on the audiometric findings of styrene-exposed workers," *Int. J. Audiol.* **50**, 652–660.

Qiu, W., Davis, R. I., and Hamernik, R. P. (2007). "Hearing loss from interrupted, intermittent, and time-varying Gaussian noise exposures: The applicability of the equal energy hypothesis," *J. Acoust. Soc. Am.* **121**(3), 1613–1620.

Qiu, W., Hamernik, R. P., and Davis, R. I. (2013). "The value of a kurtosis metric in estimating the hazard to hearing of complex industrial noise exposures," *J. Acoust. Soc. Am.* **133**(5), 2856–2866.

Rawool, V. W. (2016). "Auditory processing deficits due to exposure to Ototoxins," in *Auditory Processing Deficits*, edited by V. W. Rawool (Thieme, New York), pp. 430–437.

Rawool, V. W., and Dluhy, C. (2011). "Auditory sensitivity in opiate addicts with and without a history of noise exposure," *Noise Health* **13**(54), 356–363.

Sliwiska-Kowalska, M., Zamysłowska-Szmytko, E., Szymczak, W., Kotyło, P., Fiszler, M., Wesolowski, W., and Pawlaczyk-Luszczynska, M. (2003). "Ototoxic effects of occupational exposure to styrene and co-exposure to styrene and noise," *J. Occup. Environ. Med.* **45**(1), 15–24.

StataCorp. (2013). "Stata Statistical Software: Release 13," StataCorp LP, College Station, TX.

Thiery, L., and Meyer-Bisch, C. (1988). "Hearing loss due to partly impulsive industrial noise exposure at levels between 87 and 90 dB(A)," *J. Acoust. Soc. Am.* **84**(2), 651–659.

Venet, T., Rumeau, C., Campo, P., Rieger, B., Thomas, A., and Cour, C. (2011). "Neuronal circuits involved in the middle-ear acoustic reflex," *Toxicol. Sci.* **119**, 146–155.

Vyskocil, A., and Drolet, D. (2010). "Mixie: Mixtures of substances in the workplace: Computer-based tool for evaluating the chemical risk (calculation of the Rm)," IRSST, available at <http://www.irsst.qc.ca/mixie/?en> (Last viewed 19 June 2017).

Vyskocil, A., Drolet, D., Viau, C., Lemay, F., Lapointe, G., Tardif, R., and Gerin, M. (2007). "A web tool for the identification of potential interactive effects of chemical mixtures," *J. Occup. Environ. Hyg.* **4**(4), 281–287.

Wathier, L., Venet, T., Thomas, A., Nunge, H., Bonfanti, E., Cosnier, F., Parietti-Winkler, C., Campo, P., Tsan, P., Bouguet-Bonnet, S., and Gansmüller, A. (2016). "Membrane fluidity does not explain how solvents act on the middle-ear reflex," *Neurotoxicology* **57**, 13–21.

White, H. (1980). "A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity," *Econometrica* **48**, 817–838.

World Medical Association. (2013). "World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects," *JAMA* **310**(20), 2191–2194.

Zhao, Y. M., Qiu, W., Zeng, L., Chen, S. S., Cheng, X. R., Davis, R. I., and Hamernik, R. P. (2010). "Application of the kurtosis statistic to the evaluation of the risk of hearing loss in workers exposed to high-level complex noise," *Ear. Hear.* **31**, 527–532.