Retrospective Cohort Study of Pure Tone Audiometry Threshold Shifts from Ototoxic Substance, Continuous Noise, and Impulse Noise Exposures at Tinker Air Force Base from 2005 to 2019

Marc J. Blair

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Marc J. Blair, Major, USMC

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Abstract

This retrospective cohort epidemiology study sought to establish the comparative risks and potential indicators of hearing loss associated with combinations of ototoxic substances, impulse noise, and continuous noise exposure. Currently, there is not an existing model or methodology in the Department of Defense (DoD) that joins occupational exposure data and pure tone audiometric data. After developing an integrated database model for Tinker Air Force Base, the largest of three depot installations within Air Force Material Command, 2,372 individuals were grouped into eight combinations of exposure groups with a minimum three years exposure duration to hazards. The incidence rates and relative risk of hearing loss indicators were calculated with five different pure tone audiometry evaluation methods. With the NIOSH Significant Threshold Shift criteria, a significant increase in risk occurred in the left ear at 2,000 Hz for the Metal/Solvent/Continuous exposure group (RR=2.44 CI 1.24-4.83) compared to a continuous noise only reference group. Further descriptive and inferential statistical analysis confirmed a significant difference (Bonferroni adjusted p-value=0.023) in hearing threshold shifts in the left ear at 2,000 Hz between this exposure group and reference exposure group. In the presence of continuous noise exposure, ototoxic effects on hearing loss could only be observed in the 1,000 and 2,000 Hz frequencies. Due to data availability, researchers could not establish further confidence in results with descriptive statistical analysis or logistic regression. Results indicate the current DoD Hearing Conservation Program's significant threshold shift criteria potentially do not capture the increased risk of hearing changes from ototoxic substance exposure.

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I. Introduction

1.1 Background

Traditionally noise exposure, both continuous and impulse, is the primary factor associated with occupational hearing loss. However, growing research indicates that ototoxic substances commonly found in occupational settings could potentially affect hearing loss independently, additively, or synergistically when combined with noise exposures. In response to this research, the American Conference of Governmental Industrial Hygienists (ACGIH) adopted the "OTO" notation for potential ototoxic substances in the organization's 2019 Threshold Limit Values (TLV) publication and the United States Department of Defense (DoD, 2019) directed services to evaluate ototoxic exposures to determine their relation to the risk of occupational hearing loss. Despite the growing body of knowledge, it is unclear what effect ototoxic substances have on hearing loss, there are no established occupational exposure limits (OEL) based on hearing loss risk, and DoD specific epidemiology studies are limited.

The DoD has a significant prevalence of hearing loss illness, leading to increased disability costs and adverse effects on worker quality of life. In Fiscal Year (FY) 2017 and 2018, the United States Department of Veterans Affairs (VA) reported tinnitus and hearing loss as contributing to 16% of new service-connected claims and totaling 12% of approximately 23 million total VA service claims (VA, 2018) (VA, 2019). While specific VA payments for auditory disabilities are not published, it is reasonable to assume that based on the number prevalence of hearing loss, they likely constitute a large portion of the 70 billion dollars paid in FY2017 and FY2018 service-connected compensation. The United States Centers for Disease Control (CDC, 2016) estimates that occupational hearing loss is the most common work-related illness, and exposure to hazardous noise impacts approximately 22 million workers. While a reduction in auditory disabilities could enable substantial cost savings for the United States government and industry, mitigating auditory disabilities is a vital social responsibility to maintain worker health and quality of life because auditory disabilities, such as tinnitus and hearing loss, are irreversible.

The United States Department of Defense (DoD, 2019) Hearing Conservation Program (HCP) attempts to mitigate hearing loss by directing HCP enrollment for workers exposed to sound pressure levels (SPL) above the eight-hour time-weighted average (TWA) of 85 decibels A-weighted (dBA) for continuous noise and 140 peak unweighted pressure (dBP) for impulse noise. A vital component of the DoD HCP program is the requirement to monitor these exposed individuals with pure tone audiometric testing to mitigate incidences of hearing loss through the calculation of significant threshold shifts (STS). Despite these efforts, there is a potential gap in HCP effectiveness because auditory disability may be more complicated than the HCP components that involve only achieving acceptable continuous noise levels <85 dBA, implementation of personal protective equipment, or controlling impulse noise below 140 dBP. Growing research indicates ototoxic substances, chemicals that impact the hearing organs, may have combined effects with continuous noise exposure. Additional exposure to impulse noise, peak noises that are less than one second in duration (ACGIH, 2018), may further increase those combined effects. Therefore, concomitant exposures to continuous noise, impulse noise, and ototoxic substances could potentially be leading to increased incidence rates of auditory disability in the DoD.

Ototoxic substance exposure is a potential gap in the current evaluation of hearing-related hazards, and research has indicated that ototoxic substances could impact an individual's hearing thresholds (Campo et al., 2009). These ototoxic substances include solvents and metals, such as cadmium, lead, toluene, and xylene that DoD personnel are likely to encounter during the operation and maintenance of equipment. Previous DoD research (Schaal et al., 2018), supports this claim through the identification of increased hearing loss in shipyard workers associated with high exposure to ototoxic substances in addition to high levels of continuous noise. Outside of the DoD, the Occupational Safety and Health Administration (OSHA, 2018) and American Conference of Governmental Industrial Hygienists (ACGIH, 2018) have published ototoxic substance advisories, but current regulatory hearing protection statutes do not include ototoxic substance monitoring or specific occupational exposure limits. Increasing the effectiveness of the DoD HCP program may require the inclusion of these potentially ototoxic substances to protect hearing health effectively.

1.2 Problem

The lack of established ototoxic substance-specific occupational exposure limits and knowledge of combined effects from combinations with continuous or impulse noise exposure requires additional epidemiological research to focus limited government resources. Recent updates to the DoD HCP (DoD, 2019) direct components to assess the interactive effects of noise and ototoxic substance exposure, but specific substances of concern or methodologies are not detailed. There is a need to inform future DoD efforts to maximize limited resources both in industrial hygiene sampling efforts and hearing conservation program assignments. Understanding the interactive effects of ototoxic substances and noise requires a model to match an individual's occupational exposures of interest to pure tone audiometric data to determine potentially casual relationships. Currently, occupational and audiometric records are available separately but not in an integrated model for focused research. A study is necessary to identify the optimal integration of databases for the evaluation of exposures and health outcomes.

1.3 Justification

This retrospective cohort epidemiology study seeks to establish the comparative risks and potential indicators of hearing loss associated with combinations of ototoxic substances, impulse noise, and continuous noise exposure. Currently, there is not an existing model or methodology that joins occupational exposure data from the Defense Occupational and Environmental Readiness System – Industrial Hygiene (DOEHRS-IH) and pure tone audiometric data from Defense Occupational and Environmental Readiness System – Hearing Conservation (DOEHRS-HC). An integrated data model can provide clarity regarding potential exposure combinations with excessive risk compared to continuous noise exposure alone. A data model may also assist in identifying threshold shift warning signs for utilization in hearing conservation programs. The results of this research could direct future DoD efforts and inform resource allocation to effectively mitigate occupational injury.

1.4 Assumptions

Researchers assume DOEHRS-IH and DOEHRS-HC, the sources of data in this research, follow sufficient data quality control and assurance methods that accurately capture both occupational exposures and audiometric test data. Even with the assumption of adequate data quality management implementation, current DoD exposure assessment strategies seek to maximize limited resources to manage prioritized risks, and this approach can limit confidence in causal relationship analysis. In particular, DOEHRS-IH utilizes an exposure assessment strategy that groups workers in exposure profiles, called Similar Exposure Groups (SEG), with similar tasks, processes, materials, and time parameters (AIHA, 2015). Misclassification or omission of any SEG attribute can have cascading effects on exposure assessment strategies. These strategies can be highly variable in quality due to the usage of surrogate data, direct reading instruments, professional judgment, modeling, or limited individual sampling. Therefore, a fundamental study assumption is that researchers can derive individual exposures from the accurate assignment of personnel to SEGs. It was also assumed that different exposure assessment strategies, such as professional judgment, modeling, and actual sampling, did not bias or result in inaccurate exposure assessments.

1.5 Methodology

Researchers determined the creation of a single exposure and health effects record for each individual was the optimal method for assessing the potential interactive effects of ototoxic substances, impulse noise, and continuous noise. Despite the regular usage of DOEHRS-IH and DOEHRS-HC, there is not a direct linkage between systems, and a model is required to determine exposures and health effects. Utilizing data from DOEHRS-IH and DOEHRS-HC limited to the years 2005 to 2019, individual records were constructed independently from each database, combined, and then grouped by combinations of exposure. After grouping by study exposure group, researchers determined relative risk utilizing multiple pure tone audiometry evaluation criteria, conducted a statistical analysis to determine differences between groups, and constructed regression models. Researchers conducted this analysis to illuminate excess risks and determine the audiometric testing frequencies with significant differences.

Initial record construction from DOEHRS-IH and DOEHR-HC required extensive programming efforts to create relevant individual records. Researchers created individual exposure records utilizing SEG exposure assessment evaluations and personnel assignments with DOEHRS-IH data. Due to incomplete exposure assessments, exposures of interest could only currently be evaluated as dichotomous exposure variables, exposed or not exposed to substances of concern. Determination of an individual's health outcome utilized criteria to select an individual's first audiogram record and final audiogram record to calculate a threshold shift record. Calculations for threshold shifts utilized both unadjusted and OSHA age-adjusted frequency threshold values to identify if age was a confounding factor. This research only considered an individual eligible for the cohort if they demonstrated normal hearing on the selected first audiogram record in the research sample. Using a database joining process that excluded DOEHRS-IH exposures outside of established DOEHRS-HC audiogram dates, researchers then created a single database with a single record for each qualifying individual.

Following the creation of a combined single data source, researchers evaluated the relative risk of hearing loss by study exposure groups utilizing individual or aggregated frequency threshold values and shifts. The threshold values and shifts utilized by researchers included DoD, OSHA, and NIOSH indicators of hearing loss. Additionally, relative risk comparisons included analysis of data using both unadjusted and OSHA age-adjusted thresholds. Study exposure group data was then exported for statistical analysis utilizing Python (Python Software Foundation, Fredericksburg, Virginia) to qualitatively and quantitatively describe data. Based on the descriptive analysis, researchers determined if there were statistical differences across 500, 1000, 2000, 3000, 4000, and 6000 center band individual frequencies and aggregated frequencies between study exposure groups. Lastly, study exposure group factors such as gender, age, duration of noise exposure, and duration of audiogram monitoring were input into regression models to determine factors of significance in predicting STSs.

1.6 Specific Aims

Research Question: Does individual exposure to combinations of ototoxic substances, continuous noise, and impulse noise differ in the development of hearing loss indicators?

Specific aim#1: Identify the optimal usage of existing DOEHR-IH and DOEHRS-HC data to create individual longitudinal exposure records.

Specific aim #2: Determine the incidence rates associated with exposure groups and the relative risk between them for the development of hearing loss.

Specific aim #3: Determine threshold shifts across and at each audiogram frequency to determine statistical significance and trend shifts.

II. Literature Review

2.1 Chapter Overview

The purpose of this literature review is to establish a framework for conducting a retrospective cohort epidemiology study and supporting the interpretation of potential causal relationships in the study results.

2.2 Epidemiology

Epidemiology is the study of disease distributions in a population and the factors influencing and determining the observed distribution (Gordis, 2014). Epidemiology studies can illuminate causal relationships between exposures, assessed in this study as ototoxic substances, continuous noise, and impulse noise, and the development of a disease, hearing loss, to inform disease prevention and public health policy development (Gordis, 2014). Assessment of casual interferences is appropriate when the following standard criteria are met: (Lilienfeld and Stolley, 1994:263):

- Strength of association
- Consistency of the observed association
- Specificity of the association
- The temporal sequence of events
- Dose-response relationship
- Biological plausibility of the observed association
- Experimental evidence

Retrospective cohort studies, such as this research, rely on unbiased and accurately recorded exposure data, an understanding of physiology and toxicology studies, and other data from historical epidemiology studies to meet the criteria for inferring causal relationships. This literature review will establish the criteria necessary for causal inferences by first establishing the biological plausibility of hearing damage and specificity of the association through a review of the physiology of the ear and exposure mechanisms of action. Next, literature supporting the fulfillment of the remaining standard criteria for continuous noise, impulse noise, and ototoxic substances was identified. The results of the literature review were utilized to develop a methodology to review the strength and consistency of the observed association.

2.3 Physiology of the Ear

A basic understanding of the physiology of the ear is necessary to understand the potential toxicological mechanisms of action for the exposures evaluated in this study and the methods for evaluating changes in individual hearing thresholds. The ear is composed of three primary systems: the outer ear, middle ear, and inner ear. As a system of systems, the ear converts sound pressure waves, kinetic energy, to electrical signals that are processed by the brain. Temporary or permanent damage to specific subsystems can have cascading effects that impact an individual's hearing level thresholds.

The outer or external ear is composed of the pinna and auditory canal that direct pressure changes in the air to the middle ear for processing (Berne and Levy, 1998). Despite its size, the pinna, the most visible portion of the ear located on the sides of the head, has proven to have little role in sound funneling and primarily serves as a localization mechanism (Gelfand, 2004). After passing through the pinna, the auditory canal limits and amplifies the frequencies of sound passed to the middle ear (Berne and

Levy, 1998). Separating the outer and middle ear is the tympanic membrane that connects to the inner ear via the ossicular chain.

The middle ear contains the connecting mechanism between the tympanic membrane and the oval window of the cochlea located in the inner ear (Moore, 2003). This connecting mechanism called the ossicular chain serves as an "impendence-matching transformer" for air to cochlear fluids and consists of three small bones, the malleus, incus, and stapes (Moore, 2003). These bones have small muscles that can contract to reduce the transfer of audible sounds or reduce frequency masking (Moore, 2003).

The inner ear component utilized for hearing is called the cochlea. The cochlea consists of three fluid-filled chambers: the scala media, scala vestibuli, and scala typmani (Gelfand, 2004). When the ossicular chain transmits energy into the inner ear fluid, via the oval window, energy passes from the scala vestibuli through the scala media to the scala tympani (Berne and Levy, 1998). The transfer of energy through the scala media stimulates hair cells located in the organ of Corti. These hair cells are organized into three rows of outer hair cells (OHC), composed of 15,000 OHCs, and one row of inner hair cells (IHC) containing 3,500 IHCs (Berne and Levy, 1998). The tonotopical organization of hair cells results in higher frequency response at the base of the cochlea and lower frequency response towards the apex of the cochlea. Hair cells are connected to the brain by the eighth cranial nerve consisting of 32,000 afferent fibers, with 90% of the fibers terminating on IHCs. (Berne and Levy, 1998).

As a system, the normal human ear is sensitive to pure tones from 20 to 20,000 Hz, but only the frequencies from 300 to 3,000 Hz are vital for speech perception (Roeser et al., 2000). The intensity of sound pressure levels (SPL) processed by the ear is measured utilizing the dimensionless unit called a decibel (dB) (Gelfand, 2004). Deriving decibels requires determining the mathematical relationship between the measured sound pressure of a source (P) and a reference sound pressure level (P_0) of 2x 10^{-4} N/m^2 that represents the theoretical threshold of human hearing (Equation 1) (Gelfand, 2004).

Equation 1.

$$SPL_{dB} = 20 * \log(\frac{P}{P_0})$$

In occupational hazard assessments, decibels are measured at 1/3 octave bands, a range of frequencies named for the center band, and frequency weighted via A, C, or Z scales to assess noise sources or design noise controls (Bruce et al., 2011:668). The A-weighted decibel (dBA) closely approximates the sensitivity of the human ear and is commonly applied in assessing occupational environments (Bruce et al., 2011:668). Pure tone audiometry utilizes a different set of reference pressure levels for each center frequency to enable the diagnosis of individual hearing thresholds and is further discussed in the hearing test portion of this review.

The ear has few protective mechanisms to prevent mechanical damage from high sound pressure levels. A mechanical form of protection is the middle ear acoustic reflex, which is a contraction of the intratympanic muscles to reduce the energy transferred through the ossicular chain to the inner ear (Gelfand, 2004:50). A lesser understood protection mechanism is the various roles of the olivocochlear efferent system in protecting the inner ear (Guinan, 2018). This lack of protective mechanisms makes humans susceptible to various forms of hearing loss in an industrial environment.

2.4 Hearing Loss

Otologic disease and disorders are categorized as: congenital, infectious, inflammatory, traumatic, neoplastic, and idiopathic (Ackley, Decker, and Limb, 2007 :14). The inclusion of each in assessing the validity of an individual's occupational hearing loss is beyond the scope of this epidemiology study, but it is essential to understand that undiagnosed diseases increase the potential for confounding factors impacting the strength of association in research results. In addition to otologic disease type, hearing loss can be classified by the anatomic site as conductive, sensorineural, central, functional, or mixed (Sataloff, 2006). Sensorineural hearing loss is the primary cause of hearing loss and is a result of mechanical or metabolic damage in the inner ear and the auditory nerve (Sataloff, 2006). The focus of this study is occupational hearing loss assumed to be sensorineural loss from noise or ototoxic exposures.

Noise-Induced Hearing Loss (NIHL) is a significant concern in occupational health due to its irreversible nature and adverse impacts on quality of life for affected individuals. When exposed to high levels of noise, OHC and IHC can become permanently or temporarily damaged, reducing transmissions to the brain. Typically, noise initially impacts the first row of OHCs leading to swelling through metabolic damage or mechanical damage (Sataloff, 2006). After hair cells degenerate, the nerves connected to them may also degenerate (Sataloff, 2006). Sensorineural hearing loss is typically permanent since hair cells cannot regenerate. High levels of noise can also lead to the creation of Reactive Oxygen Species (ROS) that lead to cell death in the cochlea, but these mechanisms are not as well understood (Henderson et al., 2006).

Due to the prevalence of high levels of continuous noise in society, continuous noise above 85 dBA has been thoroughly researched and regulated. NIHL is most prevalent in the 3,000, 4,000, and 6,000 Hz frequencies, referred to as the "noise notch," and then spreads to 1,000 and 2,000 Hz frequencies (Ackley, Decker, Limber, 2007:287). This loss is a subtle and gradual process occurring primarily in the first ten years of exposure (Ackley, Decker, Limber, 2007:287). NIHL can be grouped as either permanent threshold shifts or temporary threshold shifts. Permanent threshold shifts, irreversible changes in hearing, result from either gradual loss over time or immediate loss from exposure to high energy sound (Ackley, Decker, Limber, 2007). Before a permanent threshold shift, an individual will likely experience a temporary threshold shift where hearing can recover to previous threshold levels within 24 hours (Ackley, Decker, Limber, 2007:288).

Presbycusis, age-related hearing loss due to degeneration or genetics, is another cause of hearing loss relevant to this study, but the causes are not well understood (Ackley, Decker, Limber, 2007:288). Presbycusis typically occurs in individuals older than 60, with the primary complaint of patients focused on understanding speech and not difficulty hearing (Sataloff, 2006). Although OSHA allows age adjustments, NIOSH has determined age adjusting audiogram results are likely to either over or underestimate hearing loss because age adjustments only reflect the distribution of hearing loss in society at a specific point in time (NIOSH, 1998). Despite the various causes of hearing loss, only a few audiometric tests are utilized to evaluate thresholds shifts or determine the location of the injury.

2.5 Hearing Tests

Pure Tone Audiometry (PTA) is utilized to make an initial diagnosis of hearing sensitivity and potential hearing loss (Roeser et al., 2000). As mentioned in the review of ear physiology, the ear is more sensitive to sound at frequencies in the 300 to 3,000 Hz range. Similar to the concept of dB A-weighting, the ear's sensitivity varies by frequency, and PTA utilizes this variation to establish the dB Hearing Level (dB HL) at center octave bands from 125 Hz to 8,000 Hz (Roeser et al., 2000). An individual's dB HL at evaluated frequencies is defined as a 50% response at the lowest measured value in relation to the pressure sensitivity of a normal ear (Roeser et al., 2000). In the DoD, American National Standards Institute (ANSI) S3.6 details PTA reference pressures at each octave band frequency (USAF, 2016).

Numerous factors can impact PTA test accuracy. These include equipment calibration, incorrect headband or earphone adjustments, inadequate instructions, or noise in the testing area (Roeser et al., 2000). False responses, negative and positive, can also impact the results of threshold testing. False-negative responses can result from the inattentiveness of the individual being tested or malingering, and false positives can occur when an individual has developed a persistent ringing in the ears called tinnitus (Roeser et al., 2000).

Several other methods of audiology diagnosis are available but are typically used as follow on tests to PTA and not in hearing conservation programs. These include Speech Audiometry, Auditory Brain Stem Response (ABR), and Otoacoustic Emissions (OE). In Speech Audiometry, tests utilizing spoken or recorded voices provide a method to assess awareness, discrimination, and identification/recognition (Roeser et al., 2000).

Auditory Brain Stem Response, a component of auditory evoked potentials, measures the electrical activity of a series of seven waves that occur within 10 ms of stimulus to detect damage to the auditory nerve and brainstem (Roeser et al., 2000). Otoacoustic Emissions evaluate the results of a stimulus to detect hair cell abnormalities by monitoring the evoked and spontaneous otoacoustic emissions (Roeser et al., 2000). A shortfall of Auditory Brain Stem Response and Otoacoustic Emissions is they do not test hearing, but instead the abnormalities of the sensorineural system.

2.6 Continuous Noise and Hearing Conservation Programs

The USAF has historically been at the forefront of protective hearing regulations and programs. In 1948, the USAF established the first regulations to protect hearing, and Air Force Regulation 160-3 established the first service hearing conservation program in 1956 (Humes et al., 2006). It was not until 1983 that OSHA mandated all employers establish and maintain hearing conservation programs for all employees with exposures equal to or exceeding an 8-hour time-weighted average of 85 dBA (29 CFR 1910.95). The armed services continued to utilize more sensitive measures of significant threshold shifts until OSHA standards were adopted in 2004 (Humes et al., 2006). Since 1999, all services have utilized DOEHRS-HC to store and evaluate audiometric data utilized for service HCPs (Humes et al., 2006).

The current DoD Standard, Department of Defense Instruction (DoDI) 6055.12 (DoD, 2019), directs services to establish HCPs in alignment with 29 CFR 1910.95. Additionally, the 2019 DoDI 6055.12 revision included direction to evaluate the combined effects of ototoxic substances but does not specify methodology or substances of concern. Subordinate to DoDI 6055.12, Air Force Instruction 48-127 (2016) establishes the USAF Hearing Conservation Program enrollment criteria. Key AFI 48-127 HCP criteria include:

- Pure Tone Audiometry conducted by the Council for Accreditation in Occupational Hearing Conservation (CAOHC) audiologist and within ANSI S3.6-2010 standards
- NIHL is classified as either a Significant Threshold Shift (STS), Temporary Threshold Shift (TTS), or Permanent Threshold Shift (PTS).
- An STS is defined as an "average change of 10 dB or more at 2,000, 3,000, and 4,000 Hz in either ear."
- An STS can either be positive, decrease in hearing in relation to reference audiogram, or negative, improvement in hearing in relation to reference audiogram.
- A TTS is defined as "any positive STS that is not confirmed by the noise-free follow-up test."
- A PTS is defined as "any STS found on monitoring audiometry which is still present after (1 or 2) required follow-up 14-hour noise-free audiograms."
- An STS on an annual audiogram is considered a PTS if follow-up testing is not conducted within the specified time.

Evaluating HCP effectiveness is challenging due to the lack of consensus on interpreting PTA data, USAF HCP policy non-compliance, and lack of data for non-exposed groups (Rabinowitz et al., 2018) (Masterson et al., 2014) (Masterson et al., 2015) (Soderlund et al., 2016). In regards to evaluating PTA data, 29 CFR 1910.95

governs US HCP criteria and defines “standard threshold shifts” as an average change of 10 dB or more at 2,000, 3,000, and 4,000 Hz in either ear, but does not require follow up audiograms to confirm shifts. Additionally, OSHA also allows for age-specific corrections for <20 years old to >60 years old but does not mandate their usage (29 CFR 1910.95). However, the DoD does not allow for age corrections (USAF, 2016). Since 1998, NIOSH has recommended more sensitive measures by defining “NIOSH significant threshold shifts” (NSTS) as 15 dB or higher increases within any frequency at 500, 1,000, 2,000, 3,000, 4,000, or 6,000 Hz in either ear without age adjustments (NIOSH, 1998). For convenience, the acronyms OSTS (OSHA standard threshold shift) and OSTS-A (OSHA standard threshold shift age-adjusted) are adopted to differentiate DoD and OSHA threshold shift definitions (Masterson et al., 2015).

The multitude of definitions of threshold shifts can lead to challenges in comparing and interpreting the results of HCP assessments or assessing excess risk from other occupational exposures in literature. A keynote for this research is that PTA data only exists due to the requirement to monitor employees exposed above an 8-hour time-weighted average of 85 dBA. Differing STS definitions are also subject to varying accuracy in identifying hearing loss. Research indicates that the OSTS criteria result in 43% true-positive rates for one test and 57% true-positive rates for two tests (NIOSH, 1998). Although OSTS and DoD STS methods vary slightly in follow up requirements, it would be reasonable to assume the same true-positive rates for both methodologies. Comparatively, NSTS true-positive rates were approximately 40% for the first test and 70% for the second, but with the disadvantage of identifying a significantly large quantity of hearing loss after two tests, thus increasing the difficulty of program follow-up

(NIOSH, 1998). Adopting any method to assess an STS through audiogram data alone is subject to the same limitations.

Establishing an understanding of current threshold shifts in HCPs from literature provides context to the research goals of assessing expanded exposure groups. The USAF conducts internal reviews to track HCP effectiveness by publishing Annual Reports. In the most recent Annual Year (AY) 2016 review (Mckenna and Williams, 2018), assessment of shift rate prevalence for all civilian audiograms found STS ranged from 14% to 19%, and PTS ranged 10% to 15% from 2009 to 2016. Noted shortfalls in the data included the DoD requirement directing follow up audiograms and reference discrepancies. Per USAF business rules, individual non-compliance for a follow-up assessment classifies a TTS as PTS (Soderlund et al., 2016) (USAF, 2016) and USAF assessed rates of civilian employee non-compliance ranged from 30% to 50% from 2009 to 2016 (Mckenna and Williams, 2018).

Additionally, reference audiogram discrepancies impact overall STS rates and account for 0.7-3% of STS prevalence (Mckenna and Williams, 2018). Further analysis of USAF specific data found that active-duty career fields not typically associated with high-risk noise exposure or enrollment in an HCP had greater than 9% PTS rates (Soderlund et al., 2016). Thus, the recorded PTS in HCP data for the USAF is highly variable based on non-compliance and reference discrepancies.

Assessing non-military US employers, Masterson et al. (2014) utilized NSTS, OSTS, and OSTS-A to identify shift rates between industry defined by North American Industry Classification System (NAICS) codes utilizing the first valid audiogram and last two audiograms per individual. Despite the usage of non-reference audiograms for the first audiogram, the results of their research found 20% NSTS, 14% OSTS, and 6% OSTS-A prevalence rates. Even with a differing baseline audiogram methodology comparing the results utilizing OSTS definitions to the USAF AY2016 HCP highlights the results for civilian employees are similar (Mckenna and Williams, 2018). Additionally, Masterson et al. (2014) noted that relationships between methods and within industries remained consistent for all shift definitions. This consistency infers NSTS methods are likely to identify higher numbers of individuals susceptible to hearing loss (Masterson et al., 2014).

Other methods for interpreting PTA data include the utilization of "material hearing impairment" that averages hearing levels across frequencies for comparison to a specific dB HL value (i.e. >25 dB HL). The threshold for impairment has typically been defined as an average of 25 dB HL across specific frequencies (NIOSH, 1998). ISO, NIOSH, OSHA, and the Environmental Protection Agency (EPA) utilize various frequencies included in the averaged hearing levels, and currently, NIOSH recommends averaging across 1,000, 2,000, 3,000, and 4,000 Hz (NIOSH, 1998). Masterson et al. (2015) found a prevalence rate of 18% hearing loss utilizing the NIOSH definition of material hearing impairment in assessing the last audiogram available for individuals submitted for their study. While this cross-sectional approach is limited, it provides an additional resource for research comparison. Although there are various sanctioned indicators of hearing loss from continuous noise, impulse noise exposure evaluation and risk remains a subject of debate.

2.7 Impulse Noise

Impulse noise is sound less than one second in duration as a result of collisions, explosions, or the formation of shockwaves (ACGIH, 2019). Compared to continuous noise exposure, impulse noise potentially presents a more significant hazard because the middle ear acoustic reflex cannot respond quickly enough to block the abrupt peak in pressure and return to ambient pressure (Amrein and Letowski, 2012). This intense pressure change could result in the immediate death of outer hair cells by mechanical force (Hu, 2006). In an industrial setting, impulse noise sources can include the usage of riveters, shears, and hammering.

Although impulse noise is prevalent in occupational settings, quantitative evaluation of impulse noise hazards is a complex issue due to varying intense pressure level peaks, rise time, duration, and frequency of impulse waveforms (Coles et al., 1968). These attributes of impulse noise have led to a lack of consensus in the scientific community regarding the usage of the equal energy concept (NIOSH, 1998) (Rice and Martin, 1973) (ACGIH, 2018). If the equal-energy concept is accepted, most modern Sound Level Meters (SLM) may be capable of measuring impulse noise, but standard dosimeters are not valid in measuring impulse noise due to limitations in intensity thresholds and sampling intervals (Davis and Clavier, 2017). Noise dosimetry samples are critical measurements in determining the assignment of individuals to HCPs. Other studies have attempted to quantify impulse noise with the usage of the kurtosis metric (Fuente et al., 2018). Despite lack of consensus, impulse epidemiology studies were only identified for hammer forge operations and the usage of firearms under conditions not commonly found in USAF civilian workplaces (NIOSH, 2006) (Suvorov et al., 2001).

The only impulse noise model utilized by the DoD is contained in the acquisition standard, MIL-STD-1474E, that requires the usage of the auditory hazard assessment algorithm for the human (AHAAH) model. The AHAAH model attempts to replicate the complexity of the auditory system, but research has indicated the model's assumption of anticipatory, or warned, acoustic reflex may not be valid (Jones et al., 2018). As mentioned previously, this standard is designed for the acquisition of equipment unique to the military and not the commercial off the shelf equipment typically found in civilian industrial occupations. Within the USAF, occupational assessment for all impulse noise and continuous noise over 130 dB requires contacting the United States Air Force School of Aerospace Medicine for assessment (USAF, 2016). Exposure data available for this study is likely to be limited to SLMs that have been previously associated with noise "clipping" thus under-reporting impulse noise levels. Evaluation of SEGs exposed to noise becomes complex if impulse noise is not regarded to follow the equal energy rule due to the reliance on noise dosimetry in the determination of HCP enrollment. Furthermore, the introduction of ototoxic substances may invalidate the foundational assumptions of the HCP by perturbing the protective mechanisms of the ear or directly injuring hearing organs.

2.8 Ototoxic Substances

Ototoxic substances are typically organized in the following classes: Pharmaceuticals, Solvents, Asphyxiants, Nitriles, and Metals (Campo et al., 2009) (Johnson and Morata, 2010) (OSHA, 2018). The focus of this study is limited to the ototoxic solvents and metals found in occupational settings, but it is important to note potential confounding factors. In particular, a lack of medical records or interviews in epidemiology studies may enable the inclusion of individuals with known ototoxic medication usage. Ototoxicity literature has expanded significantly in the last 20 years, but ototoxic exposure limits, mechanisms of action, excess risk, and target frequencies of ototoxic substances is still unclear.

In conducting an epidemiology study, Weight of Evidence (WoE) evaluations can direct researchers through expansive toxicology and epidemiology studies to highlight potential impacts of ototoxic solvents and metals on hearing organs (Campo et al., 2009)(Vyskocil et al., 2012)(Johnson and Morata, 2010)(Morata et al., 1994). A central theme in all current ototoxic reviews is concentrations eliciting adverse audiological outcomes may be less than current OELs, and the mechanisms of action for hearing damage are unclear. In general, solvent exposure impacts hair cells in the ear, and metals affect either the cochlea or central auditory pathways (Johnson and Morata, 2010).

Campo et al. (2009) was a significant work cited in the OSHA Ototoxic Bulletin (2018) and grouped substances according to “Good,” “Fair,” and “Poor” ototoxic evidence. Occupationally relevant substances reported as “Good” included toluene, ethylbenzene, n-propyl benzene, styrene, methyl styrene, trichloroethylene, p-xylene, n-hexane, lead, mercury, tin, and germanium (Campo et al., 2009). Occupationally relevant substances reported as “Fair” included cadmium and arsenic (Campo et al., 2009). A limitation of this study is the primary reliance on animal testing data.

Vyskocil et al. (2012) expanded the ototoxic substance WoE approach by balancing human studies and animal studies that occurred near the exposure levels found in occupational environments, both with and without noise. This approach was utilized to create interaction conclusions for substances as “Ototoxic,” “Possibly Ototoxic,” "Nonconclusive," "No Evidence," and "No Documentation" (Vyskocil et al., 2012). Occupationally relevant substances classified as "Ototoxic" included lead, styrene, toluene, and trichloroethylene (Vyskocil et al., 2012). Occupationally relevant substances classified as "Possible" included ethylbenzene, n-hexane, and xylene (Vyskocil et al., 2012). The only substance determined to have an interaction with noise was toluene (Vyskocial et al., 2012). This study illuminated limited data was available that supported known or potential ototoxicity of substances near OELs and when interacting with noise.

Despite the differences between the Campo et al. (2009) and Vyskocil et al. (2012) studies, it can be assumed that occupationally prevalent substances such as toluene, styrene, xylene, n-hexane, ethylbenzene, and lead have ototoxic effects. While biologically plausible, it is necessary to establish the probability of exposure in an occupational setting. In an extrapolated self-reported cross-sectional survey of the Australian workforce, researchers estimated 66% of men were exposed to at least one ototoxic substance at any level, 57% were exposed to an ototoxic substances at probable medium to high levels, defined as measurable but below the OEL and above the OEL, and 16% were concurrently exposed to noise greater than 85 dBA TWA and probable medium to high ototoxic exposure (Lewkowski et al., 2019). Of all the reported ototoxic substances, toluene exposure was consistently the highest percentage exposure for solvents at each exposure level and with noise (Lewkowski et al., 2019). The prevalence of these ototoxic substances makes it highly likely that workers are potentially exposed to increased hearing impairment risks.

Ototoxic metals, such as cadmium and lead, found in USAF operations, have been identified as contributing to hearing loss (Roth and Salvi, 2016). However, there is an unclear relationship between lead exposure and hearing loss when considering both animal and human studies (Carlson et al., 2019). Recent animal studies found no cochlear damage and no statistical difference in ABR tests between non-exposed groups and groups exposed to combinations of lead and cadmium above the OSHA Permissible Exposure Limit (Carlson et al., 2018). With noise added as an additional exposure factor, there continued to be no statistical difference between exposure groups, but all noise-exposed groups demonstrated cochlear outer hair cell damage implicating noise as the dominating factor in hearing loss compared to ototoxic metal exposure (Carlson et al., 2018a). In contrast, a Korean cross-sectional study of humans found lead and cadmium exposures at environmental levels impacted PTA thresholds in the higher speech frequencies of 3,000, 4,000, and 6,000 Hz (Choi and Park, 2012). While lead is believed to be primarily neurotoxic and cadmium cochleotoxic (Campo et al., 2009), current studies do not support mechanism of action determination, and PTA is likely to underestimate hearing loss due to the target of higher frequencies.

The alkylbenzene family of solvents has been identified as one of the largest groups of ototoxic solvents impacting the auditory system (Johnson and Morata, 2010). Ototoxic solvents, such as styrene, trichloroethylene, toluene, and xylene, are all identified as causing hearing loss in animal studies (Crofton et al., 1994). In addition to the typical cochlear damage from ototoxic solvents, another potential mechanism of action for ototoxic aromatic solvents is the disruption of the middle ear reflex that protects the inner ear (Wathier et al., 2019). Wathier et al. (2019) identified that benzene and chlorobenzene had significant effects on the middle ear reflex but are typically not considered to target the cochlea. Conversely, solvents known to target cochlea did not show effects on the middle ear response (Wathier et al., 2019). Ototoxic reduction of the middle ear response could potentially make exposure to impulse noise a more significant contributor to hearing loss in workers.

Newer studies indicate exposure to solvents below OELs could have an adverse effect on hearing. A cross-sectional study of 161 paint manufacturing workers identified a higher prevalence of PTA hearing loss and increased auditory evoked potential latencies in workers exposed to noise below 85 dBA in combination with ototoxic substance exposure below OELs (Juárez-Pérez et al., 2014). In a cross-sectional study of manufacturing plants for fiberglass products, individuals exposed to styrene concentrations ranging from 10 ppm - 20 ppm in combination with noise levels below 85 dBA were identified as having statistical significance in noise and styrene exposure on the outcome of hearing loss compared to ANSI 3.44 reference populations using logistic regression models (Morata et al., 2011). However, in the exposure groups where noise exposures exceeded 85 dBA, continuous noise became the primary significant factor in the outcome of hearing loss (Morata et al., 2011). These studies suggest continuous noise exposure damage masks the potential effect ototoxic solvents have on hearing thresholds. Since ototoxic substance exposure alone is not a requirement for HCP enrollment, USAF personnel exposed to a variety of these substances on a daily basis are not being evaluated for shifts in hearing thresholds unless noise is also present and serving as the primary trigger for HCP entry.

Combined exposure to ototoxic solvents and continuous noise has been assessed as increasing hearing loss odds (Sliwinska-Kowalska et al., 2001) (Demet et al., 2018) (Hormozi et al., 2017) (Fuente et al., 2018) (Metwally et al., 2012). Solvents primarily impact the higher frequencies, but depending on the substance, impacts can span mid and high hearing frequencies (Sliwinska-Kowalska et al., 2001) (Hormozi et al., 2017). In contrast, Chang et al. (2006) observed in a cross-sectional study of 58 workers that concurrent exposure to noise and toluene resulted in high dB HL thresholds at 1,000 and 2,000 Hz compared to a noise only reference group. A recent meta-analysis of 15 studies with 7,530 combined subjects indicated a dose-response relationship between different levels of exposure to organic solvent mixtures and noise (Hormozi et al., 2017). Compared to a non-exposed reference group, individuals with solvent exposures at half the OEL had an Odds Ratio (OR) of 1.37 (CI 0.75-2.48) of hearing loss, and those exposed to levels higher than the OEL had an OR of 4.51 (CI 3.46-5.90)(Hormozi et al., 2017). Increasing the duration of exposure and the number of solvents present had a similar increase in OR of hearing loss (Hormozi et al., 2017). In particular, exposures lasting less than five years resulted in an OR of 1.01 (CI 0.92-1.10), indicating exposure durations below this period may not be a significant predictor of hearing loss (Hormozi et al., 2017).

Studies of exposure to impulse noise and ototoxic substances have demonstrated higher risks for hearing loss compared to groups exposed to continuous noise and ototoxic substances. In an animal study, Lund and Kristiansen (2008) identified impulse noise exposure in combination with toluene exposure resulted in a broader range of center frequency band shifts, from 4 – 24 kHz, compared to wideband noise exposure groups when tested by otoacoustic emissions. Carreres Pons et al., (2017) also conducted an animal study with carbon disulfide, an ototoxic substance not commonly found in occupational settings, and found impulse noise with ototoxic exposure was significantly more damaging than continuous noise of the same energy with ototoxic exposures. In a study of 20 workers, Fuente at al. (2018) utilized the kurtosis metric to determine the significance of impulse noise and ototoxic solvents exposure in furniture factories. Worker PTA threshold shift results remained the same for impulse noise-exposed and solvent/impulse noise-exposed groups below 4,000 Hz, but there was a significant difference in shifts at 6,000 Hz (Fuente at al., 2018). Integration of the kurtosis metric in cumulative noise exposure calculations was found to describe this interaction best and suggests the equal energy rule does not adequately capture risks when impulse noise and ototoxic solvents are present (Fuente et al., 2018). There is reason to believe the potential combined effect of ototoxic substances and impulse noise impacts current USAF personnel conducting aircraft maintenance operations.

DoD specific studies indicate synergism with noise and ototoxic substance exposure. Assessing 138 USAF subjects, hearing loss odds, defined as a 15dB shift in either ear at 1,000 to 4,000 Hz, were calculated for individuals exposed to a minimum of three years of noise and three years of jet fuel, a complex organic solvent mixture that can potentially include n-hexane, n-heptane, toluene, and xylene (Kaufman et al., 2005). This study reported a 70% increase in odds ratio when modeled in combination with noise and a minimum of three years duration exposure to jet fuel despite the exposures being estimated below OELs (Kaufman et al., 2005). Assessing civilians conducting shipyard work, Schaal et al. (2018) assessed 1,266 personnel exposed to high/low combinations of noise, ototoxic solvents, and ototoxic metals. Results identified statistically different hearing level shifts at 2,000 Hz, shifts averaged across 2,000 to

4,000 Hz, and shifts averaged across 500 to 6,000 Hz for high metal/solvent compared to low metal/solvent groups with similar noise exposures (Schaal et al., 2018).

The following ototoxic substances (Table 1) were selected for usage in this research based on OSHA's ototoxic advisory (2018), review literature (Campo et al., 2009) (Johnson and Morata, 2009) (Vyskocil et al., 2012), and the more recent literature previously described:

Table 1. Ototoxic Substances

Category	Substance
Solvent	Benzene
Metal	Cadmium
Metal	Cadmium Compounds
Solvent	Ethyl Benzene
Metal	Germanium Dioxide
Solvent	Heptane
Metal	Lead
Metal	Lead Inorganic Compounds
Metal	Mercury
Solvent	Methyl Styrene
Solvent	N-Hexane
Solvent	N-Propyl Benzene
Solvent	P-Xylene
Solvent	Styrene
Metal	Tin Organic Compounds
Solvent	Toluene
Solvent	Trichloroethylene
Solvent	Xylene

2.9 Conclusion

This chapter reviewed the major sources of information utilized to establish the validity of the inferred causal relationships between the development of hearing loss from exposure to continuous noise, impulse noise, and ototoxic substances. Before reviewing hazard-specific risks, researchers identified the biological plausibility of hearing damage through a review of the physiology of the ear and the few protective mechanisms present. Next, researchers assessed types of hearing loss likely to be developed in an occupational environment, specifically sensorineural damage from NIHL, and the audiometric tests available to evaluate the forms of hearing damage. Following the establishment of this base knowledge, researchers then explored the primary source of occupational NIHL, continuous noise, and the corresponding comprehensive worker protection program, the Hearing Conservation Program. This exploration included assessment of the detection of hearing loss indicators from ototoxic substances with STS, OSHA age-adjusted STS, NSTS, and NIOSH material hearing impairment definitions.

After a review of the thoroughly researched and regulated continuous noise exposure hazard, researchers focused on the growing literature associated with impulse and ototoxic exposure. Utilizing a limited body of knowledge, researchers then briefly discussed impulse noise exposure and the complexity of assessing exposure risks. Impulse noise exposure may not follow the equal-energy principle, and current integration into noise dosimetry measurements may underestimate risks due to equipment limitations leading to noise clipping. Researchers then evaluated ototoxic substances, metals or solvents, based on the primary weight of evidence reviews that formed the basis of the recent OSHA ototoxic substance advisory. Ototoxic substances have different mechanisms of action and target frequencies. Additionally, dose-response relationships are not understood. Both impulse noise and ototoxic substances may impact hearing, but experimental evidence is limited.

Researchers supplemented review literature with recent toxicology and epidemiology studies that identified the risks associated with combinations of exposure to continuous noise, impulse noise, and ototoxic noise. This literature review of ototoxic substances indicated impacts to hearing thresholds could span the PTA frequency from 500 to 6,000 Hz, but typically significant threshold shifts are found in the higher PTA frequencies. Additionally, there is evidence that indicates exposures below OELs may impact hearing loss rates but with limited confidence due to primarily cross-sectional study methods. Although there may be hearing loss associated with ototoxic substances, continuous noise exposure above 85dBA TWA likely masks other forms of hearing loss.

III. Methodology

3.1 Chapter Overview

The objective of this research is to determine if combinations of exposure to ototoxic substances, continuous noise, and impulse noise result in a higher risk of hearing loss and to identify statistically significant changes in hearing thresholds at tested frequencies within the range of 500 to 6,000 Hz. This chapter outlines the methodology for gathering data, joining data, assessing relative risk, and statistical analysis. This novel methodology of joining two separate data systems enabled the assessment of combinations of exposures and the resulting health outcomes. A discussion of failed model attempts is included to inform future follow on research.

3.2 Research Design

This research design utilizes quantitative and statistical analysis of combined secondary data from internal government sources. The two secondary data systems used in this research are Defense Occupational and Environmental Health Readiness System -

Industrial Hygiene (DOEHRS-IH) and Defense Occupational and Environmental Health Readiness System – Hearing Conservation (DOEHRS-HC). DOEHRS-IH is utilized to "manage occupational and environmental health risk data and actively track biological, chemical, physical health hazards and engineered nano-object processes to service members worldwide" (DHA, 2018). DOEHRS-HC is utilized to "collect, maintain, compare and report hearing conservation, hearing readiness and deployment data for DoD personnel" (DHA, 2019). Both system databases can be accessed independently through the SAP BusinessObjects Business Intelligence (BI) Platform or Defense Information Systems Agency portal. There is no connection between DOEHRS-IH and DOEHRS-HC systems, and the only shared data field with unique values is an individual's social security number (SSN). Joining the data from these systems required utilizing a unique personal identifier combined with assigned unique SEG identifiers (SEGID) to create individual exposure records for assessment and build exposure groups of interest for the study (Figure 1). Collection of DOEHRS-IH data occurred via the SAP Platform in consultation with USAF system managers, and DOEHRS-HC data was provided from USAF system managers.

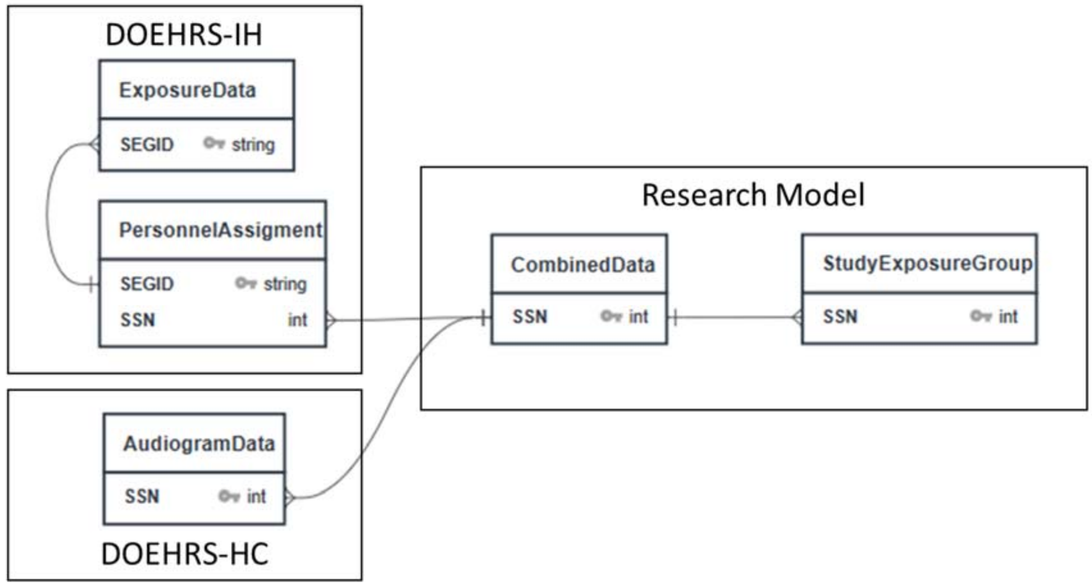

Figure 1. Basic Database Structure for Research Model

Following the creation of a combined single data source, researchers conducted a quantitative assessment of individual longitudinal exposure records for hearing threshold shifts across all frequencies unadjusted for age and with OSHA 29 CFR 1910.95 Appendix F age corrections. Individual records were assigned to study exposure groups by evaluating the duration of exposure to ototoxic substances, continuous noise, and impulse noise. For each study exposure group, Microsoft Access (Microsoft, Redmond, Washington) was utilized to count unique entries that met various PTA test conditions and organized the results into a standard "2x2" format for incidence rate and relative risks calculation. Study exposure group data was then exported for statistical analysis utilizing Python (Python Software Foundation, Fredericksburg, Virginia). Based on the descriptive analysis, researchers determined if statistical differences existed across all individual frequencies and aggregated frequencies between study exposure groups. Lastly, study exposure group factors were input into linear and logistic regression models to determine factors of significance. The utilization of secondary data to construct this model and analysis was in alignment with typical retrospective cohort studies conducted in the occupational health community.

3.3 Research Questions and Hypotheses

The proposed research question for this research is establishing if individual exposure to combinations of ototoxic substances, continuous noise, and impulse noise differ in the development of hearing loss.

H_O 1: Exposure to combinations of ototoxic substances, continuous noise, and impulse noise does not significantly increase incidence rates in developing hearing loss compared to non-exposed groups.

H_a 1: Exposure to combinations of ototoxic substances, continuous noise, and impulse noise does significantly increase incidence rates in developing hearing loss compared to non-exposed groups.

H_O 2: Exposure to combinations of ototoxic substances, continuous noise, and impulse noise does not significantly increase incidence rates in developing age-adjusted hearing loss compared to non-exposed groups.

H_a 2: Exposure to combinations of ototoxic substances, continuous noise, and impulse noise does significantly increase incidence rates in developing age-adjusted hearing loss compared to non-exposed groups.

H_O 3: Exposure to combinations of ototoxic substances, continuous noise, and impulse noise does not result in significant differences in hearing level threshold changes across 500 to 6,000 Hz frequencies.

H_a 3: Exposure to combinations of ototoxic substances, continuous noise, and impulse noise does result in significant differences in hearing level threshold changes across 500 to 6,000 Hz frequencies.

H_O 4: Exposure to combinations of ototoxic substances, continuous noise, and impulse noise does not result in significant differences in age-adjusted hearing level threshold changes across 500 to 6,000 Hz frequencies.

H_a 4: Exposure to combinations of ototoxic substances, continuous noise, and impulse noise does result in significant differences in hearing level threshold changes across 500 to 6,000 Hz frequencies.

3.4 Instrumentation

Initial assessment of DOEHRS-HC and DOEHRS-IH data utilized Microsoft Excel, Redmond, Washington, to remove incomplete record entries that contained invalid or corrupt data in key data fields. Following data cleanup, Microsoft Access executed SQL queries created audiogram threshold shifts, individual exposure records, and exposure group records for follow on processing. Microsoft Excel was utilized throughout the process to automate the concatenation of strings to eliminate variability between Microsoft Access queries. Before exporting data via .xlsx format, study exposure group records were assessed with Microsoft Access to create the necessary "2x2" epidemiology tables. Python was utilized to complete epidemiology tables with confidence intervals and conduct statistical analysis of individual exposure records. Automation of the audiogram threshold calculations and exposure records ensured consistency of results by removing potential investigator bias and errors. Commonly licensed and open-source software was selected to enable future research and model modification.

3.5 Population and Sample

Researchers limited DOEHRS-HC and DOEHRS-IH data collection to Tinker Air Force Base (AFB), near Oklahoma City, Oklahoma. Tinker AFB is the site of the largest of three depot installations within AF Material Command (AFMC) and is the location of extensive maintenance activity for C/KC-135, B-1B, B-52, and E-3 airframes (USAF, 2019). These attributes made Tinker AFB highly likely to have a significant number of employees with occupational exposure to the physical and chemical hazards of interest in this study. In addition to the high probability of hazardous exposures, Tinker AFB employs approximately 26,000 military and civilian employees and therefore is likely to have a statistically significant number of records after implementation of inclusion and exclusion criteria. Before data analysis, exclusion of military records removed the possible confounding factors associated with unique military exposures and short duration temporary assignments to various locations beyond the geographical home station. The combination of a large civilian employee sample and a high likelihood of exposures of interest established Tinker AFB as the ideal sample for this study.

3.6 DOEHSR-HC Data Collection

The USAF School of Aerospace Medicine (USAFSAM) Epidemiology Consult Service Division provided all PTA tests for military and civilian personnel conducted aboard Tinker AFB from January 2005 to July 2019. The year 2005 was selected as the beginning date to align with a previous USAF cross-sectional study of threshold shifts in audiometric data (Soderlund et al., 2016). The original data contained 334,014 records and 33,374 unique individuals. The basic methodology for utilizing DOEHRS-HC data was to establish a baseline record by identifying an individual's oldest recorded audiogram and comparing it to an individual's most recent recorded audiogram following set inclusion or exclusion criteria (Figure 2). Any audiogram records with missing frequency data, multiple birthdates, or declared ear nose throat (ENT) problems were excluded. DOEHRS-HC records are organized by unilateral test entries, either left or right ear, and not bilateral tests, both left and right ear.

A brief analysis of DOEHRS-HC data confirmed numerous instances of annotated pre-deployment and post-deployment audiograms for military personnel that would indicate non-traditional occupational exposures encountered in training or combat operations. Researchers assumed civilians were a more stable population and not participating in the military reserve or guard. The selection of civilian only records reduced the total unique individuals to 17,779 personnel and 219,831 audiogram records.

Establishing an individual's baseline record was conducted by identifying the oldest matched audiogram dates with matched bilateral (left and right ear) records that met inclusion criteria. The two primary inclusion criteria required specific audiogram test types and acceptable hearing thresholds. DoD policy for utilizing established references ensures future test results are compared to a record created before an individual's exposure to noise in the workplace, thereby enabling a more accurate determination of threshold shifts. In contrast to DoD policy, either a reference or annual audiogram was accepted as a baseline record in this research. Researchers determined this deviation was acceptable because secondary inclusion criteria required an individual to have all frequency thresholds within the range of normal hearing (<25 dB HL). The baseline selection criteria increased the study sample size by including individuals whose reference audiograms occurred before the data collection timeframe but maintained quality by ensuring only those with normal hearing remained. This method has limitations, primarily acceptance of an outlier record, that will be further elucidated in the analysis.

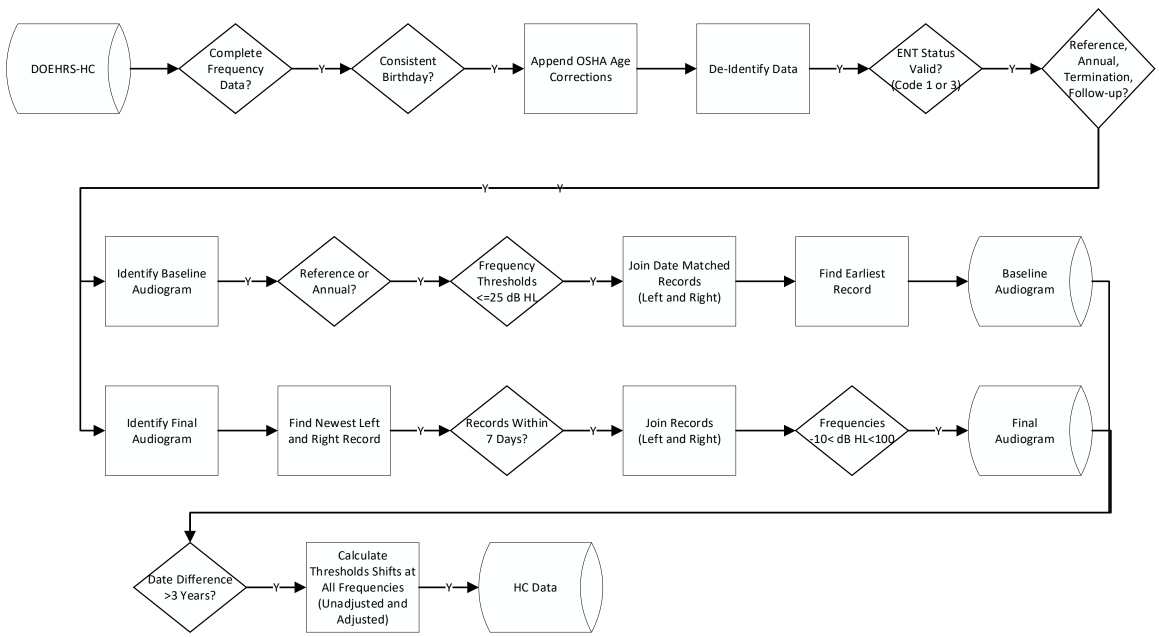

Figure 2. DOEHRS-HC Data Processing Flow Chart

An individual's final audiogram record was selected by identifying the most recent matched or unmatched date bilateral records that occurred within seven days of each other. This buffer period enabled the inclusion of audiogram records in which an individual received a follow-up audiogram on only one ear. In addition to differential dates, audiogram types were expanded from the baseline audiogram method to include annual, follow-up, termination, or reference audiograms to capture the most recent records. The final inclusion criteria for the determination of an acceptable final audiogram record evaluated frequency thresholds to ensure the recorded values were between -10 and 100 dB HL, the minimum and max values for a PTA test, to prevent erroneous record selection. This method has significant limitations compared to a careful analysis by an audiologist but enabled immediate large-scale data analysis that would otherwise be cost and time prohibitive.

Following the selection of a qualifying baseline and final record, threshold shifts at each frequency were calculated to create an individual's threshold shift record. Individual threshold shift records, grouped by an unidentifiable unique identity (IDEN), were created by subtracting the baseline audiogram thresholds from the final audiogram thresholds at each frequency, for both unadjusted and age-corrected data, and the calculated time difference between audiogram test dates in years (Table 2). Completed individual threshold shift records in the database included all data fields from original audiogram records to include audiogram test dates. After completion of this process, only threshold shift records with greater than three years of difference between the baseline and final were retained. The minimum three-year duration for determination of exposure was based on the observed time frame for ototoxic solvent health effects in the literature review. Following this methodology, a total of 4,311 unique individual threshold shift records met the criteria for model retention.

Table 2. DOEHRS-HC Threshold Shift Calculation Example

			Frequency Threshold Shift Left Ear (Hz)					
	Unique Identifier (IDEN)	Date	500	1000	2000	3000	4000	6000
Baseline	123456789	27-Jul-05	10	15	10	15	15	10
Shift	123456789	5-Oct-18	5	15	10	25	15	10
Final	123456789	13.17	-5	0	0	10	0	0

3.7 DOEHSR-IH Data Collection

DOEHRS-IH data was collected from January 2005 to October 2019, utilizing database queries created by the USAFSAM Occupational and Environmental Health Operations Division (OET) DOEHRS Support Office in the BI web portal. While utilization of the BI interface enabled ad-hoc creation of individual exposure records, significant limitations were discovered during the construction of individual exposure records and are further discussed later in the report. Three reports formed the foundation of creating individual exposure records: "Workplace Personnel Roster," "Analyze Occupational Exposure Hazards," and "Installation Noise Sample Log" (Figure 3). All reports were downloaded directly from BI utilizing the comma-separated values (CSV) file format.

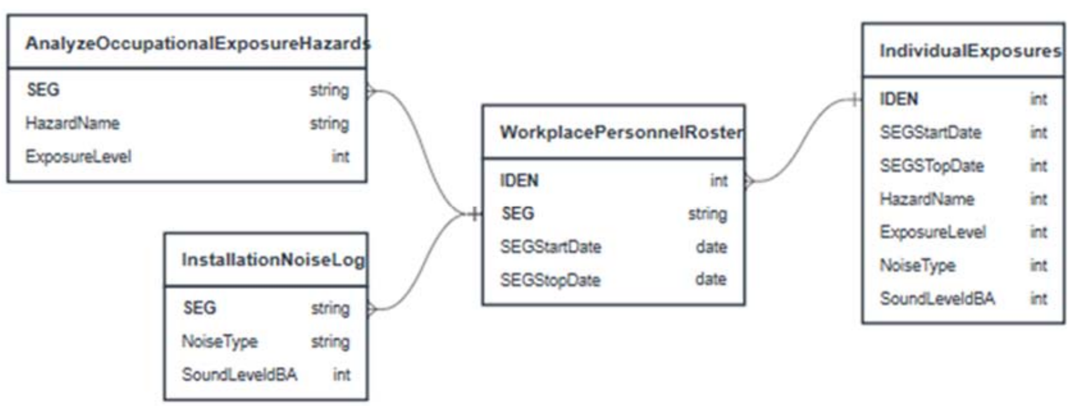

Figure 3. DOEHRS-IH Data Structure

The basic methodology for creating an individual exposure record is derived from assessments and evaluations of occupational hazards of interest assigned to a SEG (Figure 3). The determination of SEG exposure to ototoxic substances (Table 1) and continuous noise was performed via the "Analyze Occupational Exposure Hazards," and SEG impact noise exposure was determined by the "Installation Noise Sample Log" report. After identifying exposed SEGs, individual exposures mirrored SEG exposures based on individual assignments to SEGs in the "Workplace Personnel Roster." Linking these reports used the unique identifiers assigned to SEGs, i.e., "007A-Z01", as identification keys within a Microsoft Access database. Multiple SEG exposures assigned to individuals were aggregated by total exposure duration in years for ototoxic metals, ototoxic solvents, continuous noise, and impulse noise exposures. Each individual's aggregated exposure record was then joined to an individual's threshold shift audiogram for final evaluation. The only modification required for this ad-hoc utilization of reports from BI was conducting a fixed-width separation of the SEG column data in Microsoft Excel to separate the unique SEG identifier and the SEG description, i.e., "Depainting Personnel." A cornerstone assumption in this methodology is that all SEG exposures apply to all personnel assigned to the SEG regardless of the evaluation date or the personnel assignment date. Before joining databases, each report was screened for data quality and selection criteria.

The "Analyze Occupational Exposure Hazards" report determined any SEG exposure to ototoxic substances or continuous noise. Described in BI as "BE analyzed and characterized OEH hazards associated with workplaces to include the health risk estimate," this report totaled 15,738 records, 630 unique SEGs, and offered the most inclusive list of potential exposures. Modeling attempts to assess exposure through other reports, to include dosimetry and air sampling reports, revealed the inclusion of only active SEGs and exclusion of archived SEGs that constituted approximately 500 out of the total 1,110 SEGs created at Tinker AFB. Additionally, the broader range of assessment types within “Analyze Occupational Exposure Hazards” provided a more comprehensive evaluation of SEGs through the usage of professional judgment, modeling, and sampling-based assessments. Resource limitations make the sampling of every potential occupational hazard infeasible, and expansion of assessment types ensured the inclusion of potential hazards below sampling action levels. Limiting the determination of hazard exposure to reports with actual sampling was likely to underestimate the quantity of SEGs with exposures of interest. An identified shortfall of utilizing this methodology was the lack of quantitative exposure levels for the majority of non-continuous noise exposures and a portion of continuous noise exposures. This data shortfall required assessing ototoxic substances and continuous noise exposure only by dichotomous, presence or absence, exposure. After removing any records marked invalid, researchers determined SEG exposure to ototoxic substances and continuous noise exposures (Table 3).

Table 3. Sample Exposure Aggregation by Similar Exposure Group

SEG Name	Category	Substance
007A-Z01	Metal	Cadmium
007A-Z01	Metal	Cadmium Compounds
007A-Z01	Metal	Lead
007A-Z01	Continuous	Noise
007A-Z02	Continuous	Noise
007A-Z05	Metal	Cadmium
007A-Z05	Continuous	Noise
007A-Z06	Metal	Cadmium
007A-Z06	Continuous	Noise
008A-Z01	Solvent	Benzene
008A-Z01	Metal	Cadmium
008A-Z01	Solvent	Ethyl Benzene
008A-Z01	Metal	Lead
008A-Z01	Continuous	Noise
008A-Z01	Solvent	P-Xylene
008A-Z01	Solvent	Toluene
008A-Z01	Solvent	Xylene

The "Installation Noise Sample Log" report provided SEG exposure to potential impulse noise sources based on the presence or absence of keywords in the survey's qualitative description. This report provided data for individual equipment assessed at a location by SLM with dBA measurements and qualitative classification of the source as "continuous," "impact/impulse," or "intermittent." Several potential source classification discrepancies were identified based on a review of noise description comments. Attempts to gather clarification from the responsible program office were unsuccessful, and researchers utilized the description keywords "rivet," "shear," and "impact" to reclassify any matches in the 3,042-record database. Post data modification, classification of a source as "impact/impulse" determined if a SEG was considered as exposed to impulse noise. SEGs with impulse noise exposures were appended to the SEG exposure database described in the previous section. Following the completion of the SEG exposure database, researchers identified 581 SEGs as having exposures to at least one hazard of interest per continuous noise, impulse noise, ototoxic metal, and ototoxic solvent categories (Table 4).

Table 4. Number of Similar Exposure Groups with Hazards of Interest

Exposure Group	Continuous	Impulse	Metal	Solvent	Total
Continuous	X				313
Continuous_Impulse	X	X			6
Metal			X		2
Solvent				X	7
Metal_Continuous	X		X		50
Metal_Continuous_Impulse	X	X	X		4
Solvent_Continuous	X			X	105
Solvent_Continuous_Impulse	X	X		X	9
Metal_Solvent			X	X	1
Metal_Solvent_Continuous	X		X	X	76
Metal_Solvent_Continuous_Impulse	X	X		X	8

The “Workplace Personnel Roster” provided 99,752 individual SEG assignments, consisting of 19,730 unique individuals, with their respective SEG assignment start and stop times. For individuals without assignment stop times, the date of October 1, 2019, was utilized to terminate the record. Researchers observed a substantial quantity of records with SEG assignment start dates in the year 1901. In order to prevent excessive record exclusion, researchers implemented a SEG assignment modification process enabling logical record inclusion that will be detailed later in this section. Another limitation of the “Workplace Personnel Roster” report was numerous overlapping individual assignments to the same SEG, and a series of Microsoft Access queries were executed to aggregate all overlaps into one contiguous record that utilized the earliest start time and last stop time. After processing the report, researchers linked aggregated exposures to individual identifiers.

The combination of DOEHRS-IH data enabled the creation of an individual exposure record for each assigned SEG based on the evaluated list of ototoxic substances, continuous noise, and impulse noise exposures. Due to the lack of quantitative exposure value recorded in the "Analyze Occupational Exposure Hazards" report for these hazards, dichotomous exposure criteria to at least one substance per category were used to identify exposure. Estimating the duration in years of exposure to each substance category was determined as the optimal method to observe causal relationships. DOEHRS-IH and DOEHRS-HC are two unconnected systems, and before the final analysis of data by researchers, each individual's SEG assignment start and stop dates needed to be evaluated against their respective threshold record to establish temporal relationships.

3.8 Combining DOEHRS-HC and DOEHRS-IH

The combination of the two processed datasets, individual threshold shift data from DOEHRS-HC and individual exposure data from DOEHRS-IH utilizing a unique identification number, enables the analysis of combinations of exposures and subsequent hearing threshold shift outcomes to determine potential synergistic or additive relationships. Researchers needed to ensure that exposures occurred within the time frame of selected audiograms to meet the temporal relationship requirement for establishing causal relationships. The criteria utilized to select an individual's baseline audiogram record ensured that although there may have been past exposures to noise or ototoxic substances, individuals demonstrated normal hearing on the baseline audiogram date and did not have a material hearing impairment. Exposures identified in an individual’s exposure record through the processing of DOEHRS-IH data would only be relevant for establishing causal relationships if they occurred after the baseline audiogram record and before their final audiogram record. These necessary temporal relationships required modifying or excluding data from individual exposure records based on date overlaps or occurrence outside the time frame of interest.

Researchers structured a query in Microsoft Access to limit an individual's SEG assignments, and subsequently exposures, to their respective baseline and final audiogram record dates. Illustrated in Figure 4 is an example of limiting a SEG assignment for an individual whose audiograms occurred in 2007 and 2010. After evaluating each individual’s SEG assignments against audiogram dates, exposure records were either modified, removed, or accepted. SEG assignments outside initial and final audiogram dates were discarded, those intersecting were shortened if they overlapped audiogram dates, and those within the first and final audiogram dates remained unmodified. This methodology secures the temporality of events for inferred relationships.

<table>
<tr><th colspan="9">SEG Assignments Unmodified</th></tr>
<tr><td>2005</td><td>2006</td><td>2007</td><td>2008</td><td>2009</td><td>2010</td><td>2011</td><td>2012</td><td>2013</td></tr>
<tr><td colspan="4">SEG #1</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="2">SEG #2</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="5">SEG #3</td></tr>
<tr><td></td><td></td><td colspan="4">SEG #4</td><td></td><td></td><td></td></tr>
</table>

<table>
<tr><th colspan="9">SEG Assignments Modified for 2007 Baseline Audiogram and 2010 Final Audiogram</th></tr>
<tr><td>2005</td><td>2006</td><td>2007</td><td>2008</td><td>2009</td><td>2010</td><td>2011</td><td>2012</td><td>2013</td></tr>
<tr><td></td><td></td><td colspan="2">SEG #1</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="2">SEG #3</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td colspan="4">SEG #4</td><td></td><td></td><td></td></tr>
</table>

Figure 4. Example of Modified SEG Assignment Dates

Utilizing modified SEG exposure dates, researchers applied the derived SEG duration to each hazard within an individual's SEG exposure record. Data aggregation across SEGs was necessary to conduct analysis, and each exposure duration was summed by duration for continuous noise, impulse noise, ototoxic metal, and ototoxic solvent to form a singular exposure record (Figure 5). Initial modeling by researchers sought to utilize the maximum exposure level concentration, defined as MaxExpL, for each hazard, but there was a noted lack of quantitative exposure levels for the majority of non-continuous noise exposures and a portion of continuous noise exposures. Due to this data shortfall, researchers assessed ototoxic substances and continuous noise exposure only by dichotomous, presence or absence, exposure, but maintained the database coding for future research. Deconfliction of overlapping SEGs with different identification names is a limitation to this approach, but the variability of data quality and accurate individual SEG assignment outweighed continued data manipulation. Aggregated individual exposure data was then joined with threshold results for the evaluation of hearing threshold shifts.

Individual Exposures by SEG

IDEN	SEG Name	Category	ExposureDuration	MaxExpL
123456789	013A-Z02	Continuous	3.83	106.7
123456789	013A-Z02	Impact	3.83	114
123456789	013A-Z02	Metal	3.83	0.00141335
123456789	013A-Z02	Solvent	3.83	
123456789	052A-Z02	Continuous	0.17	83
123456789	052A-Z02	Solvent	0.17	
123456789	052A-Z06	Continuous	2.08	
123456789	078E-Z07	Continuous	0.58	98.4
123456789	078E-Z07	Metal	0.58	0.00425
123456789	078E-Z07	Solvent	0.58	

Aggregated Individual Exposures

IDEN	Continuous Duration	Impact Duration	Metal Duration	Solvent Duration	Continuous Max Exp	Impact Max Exp
123456789	6.67	3.83	4.42	4.58	106.7	114.0

Figure 5. Modified SEG Assignment Dates to Exposure Record Aggregation

After the creation of a single exposure and threshold shift record for each individual, researchers organized data by study exposure group to enable the evaluation of descriptive and inferential statistical differences. Researchers determined assignment to study exposure groups by a series of logic conditions utilizing a combination of exposure duration years greater than three and equal to zero (Table 5). The minimum three-year duration for determination of exposure was based on the observed time frame for ototoxic solvent health effects in literature and to maintain a sample size to support data analysis. This usage of "AND" logical conditions ensured individuals could not be assigned to multiple study exposure groups and bias analysis of results. Following the assignment of individuals to exposure groups, researchers determined that sufficient data manipulation occurred based on the limitations of data collected from DOEHRS-HC and DOEHRS-IH.

Table 5. Exposure and Threshold Shift Criteria for 3 Year Duration Age-Adjusted

Exposure	Metal	Operator	Solvent	Operator	Continuous	Operator	Impulse
Continuous	0	AND	0	AND	>=3	AND	0
Continuous_Impulse	0	AND	0	AND	>=3	AND	>=3
Metal	>=3	AND	0	AND	0	AND	0
Solvent	0	AND	>=3	AND	0	AND	0
Metal_ Continuous	>=3	AND	0	AND	>=3	AND	0
Metal_ Continuous _Impulse	>=3	AND	0	AND	>=3	AND	>=3
Solvent_ Continuous	0	AND	>=3	AND	>=3	AND	0
Solvent_ Continuous _Impulse	0	AND	>=3	AND	>=3	AND	>=3
Metal_Solvent_ Continuous	>=3	AND	>=3	AND	>=3	AND	0
Metal_Solvent_ Continuous _Impulse	>=3	AND	>=3	AND	>=3	AND	>=3
*Exposures represented in years							

3.9 Data Analysis

Following data collection and manipulation, researchers conducted quantitative epidemiology tests with Microsoft Access and statistical analysis of data with Python utilizing study exposure groups. Researchers calculated incidence rates (IRs) and relative risks (RRs) for the development of hearing loss utilizing the DoD/OSHA STS, OSHA STS age-adjusted, NIOSH STS, NIOSH Material Hearing Impairment, and 500-6000 Hz averaging PTA evaluation methods (Table 6). The utilization of multiple tests enabled researchers to identify data trends and comparison to rates found in previous research. After the determination of relative risks, confidence intervals were determined with biostatistics formulas to evaluate models. Statistical analysis focused on establishing if significant differences between the continuous noise only reference group and other exposure groups existed at each tested audiogram frequency or in regression models. Regression model analysis included logistics regression based on the development of an STS.

Table 6. Pure Tone Audiometric Evaluation Tests

Significant Threshold Shift (STS)	>=10 dB HL threshold shift average shift at 2,000, 3,000, 4000 Hz
Significant Threshold Shift Age-Adjusted (STS-A)	>=10 dB HL threshold shift age-adjusted average shift at 2,000, 3,000, 4000 Hz
NISOH Material Hearing Impairment	>=25 dB HL threshold average at 1,000, 2,000, 3,000, 4,000 Hz
NISOH Significant Threshold Shift (NSTS)	>=15db HL threshold shift at any frequency 500, 1,000, 2,000, 3,000, 4,000, 6,000 Hz
All Frequency Threshold Average	>=25 dB HL threshold average at 500, 1,000, 2,000, 3,000, 4,000, 6,000 Hz

IV. Results and Analysis

4.1 Chapter Overview

The purpose of this chapter is to analyze the data created by the integration of DOEHRS-HC and DOEHRS-IH systems in order to:

- Determine the potential for combined effects from combinations of exposure
- Validate the methodology utilized by researchers to process large volumes of data
- Establish the optimal PTA test criterion for detecting hearing loss indicators.

Utilizing study exposure groups to manage individual worker data effectively, researchers conducted an analysis with epidemiological methods, descriptive statistics, and inferential statistics to determine significant variables contributing to the development of hearing loss indicators. Concurrently, this epidemiological analysis included the evaluation of modeled PTA test rates against published data to determine the validity of the research methodology's baseline audiogram and last audiogram selection criteria. Lastly, researchers linked all analyses to support a recommendation for the optimal PTA evaluation criteria for assessing ototoxic substance effects on hearing loss.

4.2 Study Population and Exposure Groups Characteristics

The final study population consisted of 2,372 individuals organized into eight exposure groups composed of various combinations of exposure to ototoxic substances, impulse noise, and continuous noise. Analysis of the study population and exposure groups was conducted to ensure a sufficient sample size for each group existed for biostatistics, inferential statistical analysis, and comparison of descriptive statistic variables between exposure groups. The size of each exposure group ranged from 12 to 872 personnel, with the majority of smaller exposure groups, n<50, containing impulse noise conditions (Table 7). Due to the quality of impulse noise exposure assessments encountered by researchers and the necessary modification of impulse noise source data, this finding was expected by researchers. The small sample size for these impulse noise-exposed groups was below the central limit theorem minimum size to establish normalcy, n<50, and therefore future analysis focuses sparingly on these groups. After disregarding smaller exposure groups, the remaining group sizes ranged from 266 to 872 personnel (Table 7). A requirement for 133 individuals in both the unexposed and exposed groups was determined as necessary to achieve an 80% study power with EpiInfo StatCalc (Dane et al., 2011) utilizing a 14% prevalence of an STS for USAF civilians (McKenna and Williams, 2014) as a surrogate incidence rate for the continuous noise only reference group, a RR=2 for ototoxic exposures, a ratio of 1:1 for unexposed to exposed group sizes, and α=0.05.

The largest exposure group containing 872 personnel was the combination of ototoxic metals, ototoxic solvent, and continuous noise exposures. Of the 2,373 individuals in the study population, individuals exposed to ototoxic substances totaled 2,041 individuals and constituted approximately 86% of the study population. These results indicate that ototoxic substance exposure is highly prevalent in the civilian employee population assigned to the HCP at Tinker AFB. Based on this observation and a review of the literature, there is a potential that continuous noise exposures are masking the hearing loss from ototoxic substances in the present study (Morata et al., 2011).

Table 7. Exposure Group Gender Distribution

SEG	Male	% Male	Female	% Female	Total
Continuous	264	85%	46	15%	310
Continuous_Impulse	18	86%	3	14%	21
Metal_Continuous	230	86%	36	14%	266
Metal_Continuous_ Impulse	10	83%	2	17%	12
Solvent_Continuous	437	89%	54	11%	491
Solvent_Continuous_ Impulse	45	94%	3	6%	48
Metal_Solvent_Continuous	774	89%	98	11%	872
Metal_Solvent_Continuous_ Impulse	315	89%	37	11%	352
Total	2093	88%	279	12%	2372

Identification of approximately similar demographics and exposure values for study exposure groups were necessary to establish causal relationships and identify potential confounding factors. DOEHRS-IH and DOEHRS-HC data are not collected for research purposes, and therefore demographics assessed by researchers include only the gender and age distributions of exposure groups. The study population was 88% male and 12% female with study exposure groups gender demographics predominantly within +/- 3% of the overall averages (Table 7). The largest percentage of females in a significantly sized exposure group was the continuous noise only group with a 15% female composition. Researchers noted that the lower representation of female workers could potentially make gender a significant independent variable in inferential statistical analysis.

Researcher analysis of age demographics was conducted by assessing averages of exposure groups and categorization of data by age groups. The average age of the total population was 44.7 years (standard deviation 10.2), and each exposure group was approximately similar except for the continuous noise only exposure group having the highest average of 47.3 years (Table 8). Next, researchers grouped values into bins of ten years to determine the distribution and identified the 38 to 47-year-old age group as the largest of the study population, consisting of 31% of the total number of workers (Table 9). Overall, approximately 85% of the study population was between ages 28 to 57, and the distribution of ages between study exposure groups was similar (Figure 6). Comparatively, Masterson et al. (2014) observed 78% of individuals were between the ages of 26 to 55 years old in the evaluation of PTA data by NAICS, thus supporting the comparison of this study to civilian workers. The single outlier in the >78 age group was verified as valid in identifiable DOEHRS-HC source data. These similar demographic attributes between exposure groups partially validated the future analysis of causal relationships by researchers.

Table 8. Exposure Group Age Average and Standard Deviation

SEG	Average (Years)	Standard Deviation
Continuous	47.3	9.3
Continuous_ Impulse	43.2	11.5
Metal_Continuous	44.8	9.6
Metal_Continuous_ Impulse	40.4	7.8
Solvent_Continuous	44.6	10.8
Solvent_Continuous_ Impulse	41.7	9.6
Metal_Solvent_Continuous	44.2	10.1
Metal_Solvent_Continuous_ Impulse	44.3	10.7
Total	44.7	10.2

Table 9. Exposure Group Age Stratification

	Age Groups							
SEG	18-27	28-37	38-47	48-57	58-67	68-77	>78	Grand Total
Continuous	4	52	100	123	29	1	1	310
Continuous_Impulse	2	5	7	3	4			21
Metal_Continuous	8	65	90	78	25			266
Metal_Continuous_ Impulse	1	3	5	3				12
Metal_Solvent_Continuous	24	254	283	217	89	5		872
Metal_Solvent_Continuous_ Impulse	11	107	101	89	42	2		352
Solvent_Continuous	31	128	136	134	62			491
Solvent_Continuous_ Impulse	2	17	18	8	3			48
Total	83	631	740	655	254	8	1	2372
Total %	3.50%	26.60%	31.20%	27.61%	10.71%	0.34%	0.04%	

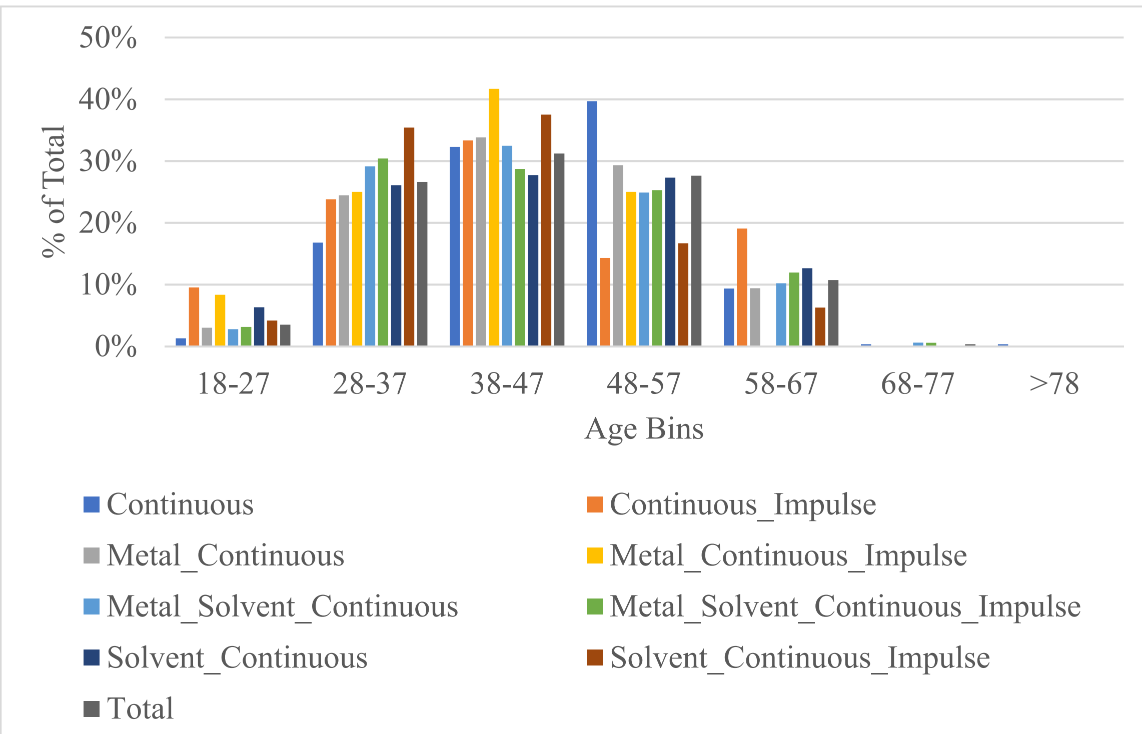

Figure 6. Age Distribution by Exposure Group

In addition to demographics, study exposure groups were assessed to ensure similar exposure group characteristics for the average time between audiograms, exposure durations to hazards, and the maximum count of unique ototoxic substance exposures per individual. The average duration in years between the established baseline audiogram and the final audiogram identified in the methodology was approximately 8.7 years (standard deviation 3.1) for the study population. Further analysis of audiogram duration by study exposure groups indicated means and standard deviations were approximately equal (Table 10). Therefore, exposure group audiogram durations were likely sufficient to demonstrate the gradual hearing loss that occurs within the first ten years of exposure to occupational noise (Ackley, Decker, Limber, 2007:287). Since this study's research methodology utilized the observed audiogram dates to determine the years of exposure to a hazard, further analysis of exposure durations was necessary to evaluate study exposure group characteristics.

Table 10. Years Duration from Baseline to Final Audiogram by Exposure Group

SEG	Mean (Years)	Standard Deviation
Continuous	8.3	3.3
Continuous_Impulse	8.4	3.1
Metal_Continuous	8.6	3.1
Metal_Continuous_Impulse	10.2	3.9
Solvent_Continuous	8.4	3
Solvent_Continuous_ Impulse	8.1	3
Metal_Solvent_Continuous	8.7	3
Metal_Solvent_Continuous_ Impulse	9.5	2.8

Researchers continued exploration of the similarities between the years of duration of exposure to hazards for continuous noise, impulse noise, ototoxic metal, and ototoxic solvent exposures to determine if sufficient exposure durations were present to incur hearing loss (Table 11). As noted in the literature review, DoD individual audiogram data is likely only available due to HCP enrollment criteria, and therefore continuous noise exposure is the only common shared exposure variable between study exposure groups. The average duration in years of exposure to continuous noise for the study population was 7.4 years (standard deviation 3.4), and exposure groups' mean values ranged from approximately 6 to 9 years. Observed differences in hearing loss by exposure group could be attributed to this variability in duration to continuous noise exposures.

Table 11. Years Duration Exposure to Continuous Noise

SEG	Mean (Years)	Standard Deviation
Continuous	6.1	3
Continuous_Impulse	6.3	2.1
Metal_Continuous	7	3.1
Metal_Continuous_Impulse	9.4	5.7
Solvent_Continuous	6.9	3
Solvent_Continuous_ Impulse	7	3
Metal_Solvent_Continuous	7.8	3.6
Metal_Solvent_Continuous_ Impulse	8.6	3.3

Further exploration of ototoxic metals, ototoxic solvents, and impulse noise was conducted to determine the mean exposures for each exposure group. Researchers observed that exposure group means by hazard ranged from approximately 6 to 8 years (Table 12). Based on the research of Hormozi et al. (2017), ototoxic substance exposure near a duration of 5 years of exposure would demonstrate an OR of hearing loss from 1.01 to 1.57 with confidence intervals without synergistic effects. Kaufman et al.'s (2018) study of workers with jet fuel exposure identified an OR of hearing loss of 1.70 (95% CI 1.14 –2.3) for three years of exposure. Therefore, researchers expected to observe relative risks near 1.0 and not definitive synergistic effects in the performance of a biostatistical analysis.

Table 12. Years Exposure to Hazards by Exposure Group

SEG	Impulse Noise		Ototoxic Metal		Ototoxic Solvent	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Continuous	N/A	N/A	N/A	N/A	N/A	N/A
Continuous_Impulse	5.9	2.2	N/A	N/A	N/A	N/A
Metal_Continuous	N/A	N/A	6.8	3	N/A	N/A
Metal_Continuous_Impulse	6.2	2.5	6.6	3.3	N/A	N/A
Solvent_Continuous	N/A	N/A	N/A	N/A	6.5	2.8
Solvent_Continuous_Impulse	5.7	2.2	N/A	N/A	6.2	2.4
Metal_Solvent_Continuous	N/A	N/A	7.2	3.1	7.2	3.3
Metal_Solvent_Continuous_Impulse	7.2	2.6	8.2	3.2	8.1	3.1

The final exposure group characteristic analysis conducted by researchers focused on determining the average maximum count of unique ototoxic metal and ototoxic substances for individuals assigned to each exposure group. This analysis was conducted post-development of the research methodology and did not utilize the SEG and audiogram "fencing" process previously described. This deviation from the research methodology was utilized in order to identify individuals who may have been exposed to ototoxic substances outside of the established baseline audiogram and final audiogram dates. Also, this methodology was important to identify if the number of ototoxicants without regard for concentration act additively or synergistically in producing hearing loss indicators. The average count of unique substances ranged from 1.5 to 3.6 for metals and solvents (Table 13). Additionally, researchers noted the highest average quantity of ototoxic metal, average 3.5, and solvent exposures, average 3.6, occurred in the Metal_Solvent_Continuous_ Impulse exposure group. Hormozi et al. (2017) found a hearing loss OR of 1.62 (confidence interval 1.07 to 2.44) from solvent exposures within 2 to 5 substances. Researchers also noted in this assessment a few individuals with previous or subsequent ototoxic exposures outside the established dates with assignments to non-exposed groups. In the case of exposures prior to an individual's audiogram dates, there is a potential for this exposure as a confounding effect, and this limitation will be further elucidated in the limitations section.

Table 13. Number of Unique Ototoxic Substances per Individual by Exposure Group

	Ototoxic Metal		Ototoxic Solvent	
SEG	Mean	Standard Deviation	Mean	Standard Deviation
Continuous	0	0.3	0	0.3
Continuous_Impulse	0	0	0.1	0.4
Metal_Continuous	1.7	0.9	0	0.2
Metal_Continuous_Impulse	1.6	0.5	0	0
Solvent_Continuous	0	0	1.7	0.8
Solvent_Continuous_ Impulse	0	0.3	2.3	0.9
Metal_Solvent_Continuous	2	0.8	2.6	1.6
Metal_Solvent_Continuous_ Impulse	3.6	0.9	3.5	1.2

In summary, the researchers' assessment of the characteristics of the study population and exposure groups identified that the majority of characteristics were approximately similar between exposure groups. The study population is predominately male (88%), and the average age of the population is 44.7 years old. These overall averages are similar between exposure groups except for the continuous noise only exposure group displaying a higher age average of 47.3 years and approximately 40% of the exposure group between the ages of 48 to 57 years old. This older age characteristic for the continuous noise only exposure group could contribute to higher rates of hearing loss due to the higher probability of increased exposure to continuous noise in the workplace and home. The average duration between the first and last audiogram for exposure groups was 8.7 years and was likely sufficient to observe hearing loss effects from occupational exposure to noise or ototoxic substances. In assessing duration in years of exposure to noise and ototoxic substances, the average duration ranged from approximately 6 to 8 years. Based on the reviewed literature, researchers were likely to expect OR of hearing loss no higher than 1.57. A retroactive assessment of the maximum count of ototoxic substances found that individuals were exposed to a range of 1.6 to 3.6 substances per their respective exposure group assignment. The research of Hormozi et al. (2017) indicates that the number of substances found in this study would likely result in an increased hearing loss OR of 1.62. Overall these study population characteristics indicate researchers are likely to see only slightly increased hearing loss effects from combinations of ototoxic substances.

4.3 Exposure Group Hearing Loss Incidence Rates and Relative Risks

Researchers utilized the various methods of pure tone audiometry hearing loss indicators identified in this study's literature review (Table 6) to conduct a biostatistical analysis of the development of hearing loss indicators in exposure groups. This approach is warranted for two reasons 1) the differing frequencies and mathematical functions utilized in each hearing test could potentially alter calculated disease development rates, and 2) the sensitivity of various test methods can change the outcome of hearing loss. In particular, PTA evaluation methods typically do not group low (500 to 1000 Hz) and high frequencies (2000 to 6000 Hz). For example, the usage of only the DoD's STS criteria, defined as a threshold shift average from 2,000 to 4,000 Hz, may under or overestimate the potential impact of ototoxic substances that impact the 500, 1,000 or 6,000 Hz octave bands. Thus, the adoption of multiple methods in assessing incidence rates was necessary to evaluate changes in hearing thresholds over the entire PTA spectrum and identify the optimal method for evaluating both exposures to noise and ototoxic substances found in the literature review.

Researchers initially assessed the risk of development of hearing loss indicators utilizing the DoD STS method. The calculated incidence rates ranged from 14% to 20% across all exposure groups (Table 14). Despite the research model usage of only one final audiogram vice the series of follow up audiograms directed by the DoD, these results are consistent with the 14% to 19% STS rates in the Air Force civilian employee population (McKenna and Williams, 2018). Additionally, these results are relatively similar to the 12% to 18% STS rates identified by Masterson et al. (2014) in the evaluation of industry by NAICS. Research model consistency with published rates validated the study objective to create a methodology that optimizes the assessment of large volumes of audiometric data. Researchers then assessed the relative risk of hearing loss indicators utilizing the continuous noise only exposure group as the reference, and the results indicated that there was a decreased relative risk, $RR<1$, for all combinations of ototoxic exposure groups. Overlooking the lack of combined effects, Solvent/Continuous and Metal/Solvent/Continuous/Impulse exposure groups had the highest RR at 0.91 and 0.92, respectively. Assessment of confidence intervals indicated there is a potential for combined effects, up to a RR of 1.27 for the Metal/Solvent/Continuous/Impulse exposure group, but due to the limited development of hearing loss indicators in exposure groups, there is insufficient data in establishing the combined effects of ototoxic substances. Researchers postulated the current DoD STS criteria might be insufficient in evaluating hearing loss from ototoxic substances by not considering effects at 500, 1,000, and 6,000 Hz frequencies.

Table 14. Incidence Rate and Relative Risk of DoD Significant Threshold Shift

Exposure	Developed	Did Not Develop	n	IR	RR	CI95L	CI95U
Continuous (reference)	61	249	310	0.2	1.0		
Continuous_Impulse	4	17	21	0.19	0.97	0.39	2.4
Metal_Continuous	38	228	266	0.14	0.73	0.5	1.05
Metal_Continuous_ Impulse	1	11	12	0.08	0.42	0.06	2.8
Solvent_Continuous	88	403	491	0.18	0.91	0.68	1.22
Solvent_Continuous_ Impulse	8	40	48	0.17	0.85	0.43	1.66
Metal_Solvent_Continuous	152	720	872	0.17	0.89	0.68	1.16
Metal_Solvent_Continuous_Impulse	64	288	352	0.18	0.92	0.67	1.27
IR- Incidence Rate, RR- Relative Risk, CI95L/U- Confidence Interval 95% Lower/Upper							

In contrast to the DoD's policy to not conduct age adjustments, researchers explored the usage of OSHA age adjustments to determine if age was a potential confounding factor in the development of hearing loss in this study. Researcher utilization of STS criteria and OSHA age adjustments yielded IRs from 6% to 9% (Table 15). Researchers assumed the IR reduction would be equal in magnitude and direction for all exposure groups given the similar age demographics within the study population, but the analysis of RR revealed the most significant decrease in rates, from 20% to 6%, occurred in the continuous noise only reference group. This reduction in IR for the reference exposure group increased the observed RR>1 for exposure groups with ototoxic substance variables, indicating possible combined effects when accounting for age. As observed in the STS method, the Solvent/Continuous and Metal/Solvent/Continuous/Impulse exposure group continued to demonstrate the highest RR for an age-adjusted STS at a RR of 1.33 and 1.44, respectively. In assessing model effectiveness and similarities to literature, researchers observed the rates of hearing loss for age adjustment were similar to the approximately 6.4% prevalence observed by Masterson et al. (2014) in assessing industries by NAICS. Despite disagreements on the application of age adjustments in literature and by NIOSH (1998), results indicate ototoxic exposures may increase hearing loss rates when accounting for age variables.

Table 15. Incidence Rate and Relative Risk of Significant Threshold Shift with OSHA Age Adjustment

Exposure	Developed	Did Not Develop	n	IR	RR	CI95L	CI95U
Continuous (reference)	19	291	310	0.06	1.0		
Continuous_Impulse	4	17	21	0.19	3.11	1.16	8.31
Metal_Continuous	17	249	266	0.06	1.04	0.55	1.96
Metal_Continuous_ Impulse	0	12	12	0.0	0.0		
Solvent_Continuous	40	451	491	0.08	1.33	0.78	2.25
Solvent_Continuous_ Impulse	4	44	48	0.08	1.36	0.48	3.83
Metal_Solvent_Continuous	57	815	872	0.07	1.07	0.65	1.76
Metal_Solvent_Continuous_ Impulse	31	321	352	0.09	1.44	0.83	2.49
IR- Incidence Rate, RR- Relative Risk, CI95L/U- Confidence Interval 95% Lower/Upper							

Following the evaluation of PTA data with DoD and OSHA evaluation criteria, researchers explored the usage of “material hearing impairment” criteria utilized in forming the basis of the 85 dBA TWA threshold for HCPs (NIOSH, 1998). This approach allowed researchers to investigate the excess risk of hearing loss in frequencies typically associated with speech discrimination (NIOHS, 1998). In contrast to the assessment of threshold shifts, the NIOSH material hearing impairment method assesses the actual threshold values against a 25 dB HL limit. Researchers observed assessment of exposure groups with the NIOSH material hearing impairment criteria yield IRs ranging from 3% to 7% (Table 16). Similar to STS and age-adjusted STS evaluation results, the Solvent/Continuous and Metal/Solvent/Continuous/Impulse exposure groups continued to demonstrate the highest relative risks of exposure group combinations, RR 1.08 and RR 1.57 respectively, but confidence intervals remained variable with RR<1 and RR>1. Despite these RRs, the IR of Metal/Solvent/Continuous/Impulse was 3% higher compared to the continuous noise group indicating a slight increase in risk. For comparison, the increased risk at age 30 from exposure to 85 dBA TWA over 80 dBA TWA for a period of 5 to 10 years is approximately 1.2% and exposure to 90 dBA TWA over 85 dBA TWA for the same duration is approximately 4% (NIOSH, 1998). Researcher assessment of literature identified model results as consistent with the estimated average 6.64% incidence rate of material hearing impairment in US industries from the years 2006 to 2010 (Masterson et al., 2015). Assuming industries with low or no ototoxic exposures are included in the Masterson et al. (2015) study, it is likely the range of calculated incidence rates in this research are within the range of shift rates from continuous noise only exposure.

Table 16. Incidence Rate and Relative Risk of Material Hearing Impairment

Exposure	Developed	Did Not Develop	n	IR	RR	CI95L	CI95U
Continuous (reference)	14	296	310	0.05	1.0		
Continuous_Impulse	3	18	21	0.14	3.16	0.99	10.15
Metal_Continuous	9	257	266	0.03	0.75	0.33	1.7
Metal_Continuous_Impulse	0	12	12	0.0	0.0		
Solvent_Continuous	24	467	491	0.05	1.08	0.57	2.06
Solvent_Continuous_Impulse	1	47	48	0.02	0.46	0.06	3.43
Metal_Solvent_Continuous	40	832	872	0.05	1.02	0.56	1.84
Metal_Solvent_Continuous_Impulse	25	327	352	0.07	1.57	0.83	2.97
IR- Incidence Rate, RR- Relative Risk, CI95L/U- Confidence Interval 95% Lower/Upper							

Next, researchers evaluated hearing impairment utilizing the integration of final audiogram threshold levels at all testing PTA frequencies. This approach allowed researchers to expand on frequencies utilized in the NIOSH material hearing impairment method by the inclusion of the 500 Hz and 6,000 Hz frequencies threshold levels. IRs from 5% to 6% (Table 17) in the present study were nearly identical to the incidence rates calculated utilizing NIOSH material hearing impairment criteria. The lack of notable change is likely a result of the threshold values at 500 Hz and 6,000 Hz averaging each other out. Researchers determined this model adds no additional value compared to the NIOSH material hearing impairment method and elected to conduct further exploration of threshold averaging of 500 to 6,000 Hz frequencies during inferential statistical analysis.

Table 17. Incidence Rate and Relative Risk of 500-6,000 Hz Frequency Average >25dB HL

Exposure	Developed	Did Not Develop	n	IR	RR	CI95L	CI95U
Continuous (reference)	16	294	310	0.05	1.0		
Continuous_Impulse	2	19	21	0.1	1.85	0.45	7.5
Metal_Continuous	9	257	266	0.03	0.66	0.29	1.46
Metal_Continuous_Impulse	1	11	12	0.08	1.61	0.23	11.19
Solvent_Continuous	26	465	491	0.05	1.03	0.56	1.88
Solvent_Continuous_Impulse	1	47	48	0.02	0.4	0.05	2.97
Metal_Solvent_Continuous	40	832	872	0.05	0.89	0.51	1.56
Metal_Solvent_Continuous_Impulse	22	330	352	0.06	1.21	0.65	2.26
IR- Incidence Rate, RR- Relative Risk, CI95L/U- Confidence Interval 95% Lower/Upper							

The last hearing loss indicator criteria explored by researchers was the NIOSH STS method. As noted in the literature review, the NIOSH STS method has a significantly higher sensitivity rate for hearing loss on the second follow up audiogram and has been recommended by NIOSH as a more sensitive indicator of hearing loss for prevention programs compared to the DoD/OSHA STS method (NIOSH, 1998). However, there is the disadvantage that the NISOH STS method potentially "tags" an excess number of cases of hearing loss in an initial audiogram, thus requiring significant follow up (NIOSH, 1998). Researcher implementation of the NIOSH STS evaluation method demonstrated significantly higher IRs, ranging from 56% to 62% compared to the continuous noise only reference group (Table 18). This significant increase in the development of hearing loss reduced confidence interval ranges, and combined effects were identified for the first time for all ototoxic substance exposure groups (Figure 7). Analysis of RR identified the Metal/Solvent/Continuous/Impulse exposure group as possessing the highest RR at 1.12 with a confidence interval from 0.99 to 1.27. Researchers postulated the incidence rates determined by the NIOSH STS are potentially more sensitive in the evaluation of ototoxic effects because of the inclusion of the 500, 1,000 and 6,000 Hz frequencies and the usage of absolute shifts by independent frequency vice averaging values. For example, Chang et al. (2006) identified concomitant exposure to toluene and noise increased hearing thresholds at the 1,000 and 2,000 Hz frequencies, and Fuente et al., (2018) observed significant changes at 6,000 Hz for concomitant exposure to impulse and solvent-exposed workers. Researchers selected this method for further exploration to determine the IRs of hearing loss at each octave band center frequency for each ear.

Table 18. Incidence Rate and Relative Risk of NIOSH Significant Threshold Shift

Exposure	Developed	Did Not Develop	n	IR	RR	CI95L	CI95U
Continuous (reference)	173	137	310	0.56	1.0		
Continuous_Impulse	9	12	21	0.43	0.77	0.46	1.27
Metal_Continuous	154	112	266	0.58	1.04	0.9	1.2
Metal_Continuous_Impulse	6	6	12	0.5	0.9	0.5	1.59
Solvent_Continuous	281	210	491	0.57	1.03	0.9	1.16
Solvent_Continuous_Impulse	29	19	48	0.6	1.08	0.84	1.39
Metal_Solvent_Continuous	493	379	872	0.57	1.01	0.9	1.14
Metal_Solvent_Continuous_Impulse	220	132	352	0.62	1.12	0.99	1.27
IR- Incidence Rate, RR- Relative Risk, CI95L/U- Confidence Interval 95% Lower/Upper							

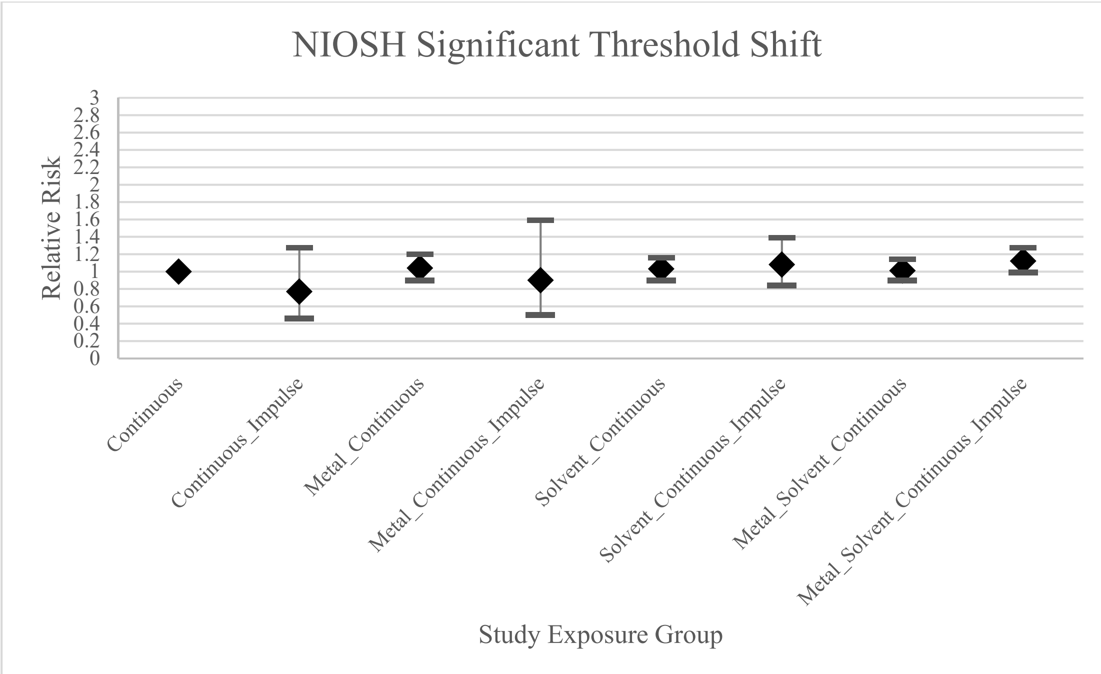

Figure 7. Relative Risk for NIOSH Significant Threshold Shift

Researchers determined the demonstrated relative risks and smaller confidence intervals in the assessment of the NIOSH STS method required further analysis. In order to conduct this analysis, researchers assessed exposure groups by the incidence rates of a NIOSH threshold shift (>15 dB HL) at each octave band center frequency for the left (Figure 8) and right ear (Figure 9). Researchers observed the characteristic notch attributed with NIHL (Ackley, Decker, Limber, 2007:287) as reflected by higher incidence rates of NIOSH STS at the 3,000, 4,000, and 6,000 Hz frequencies in both ears. Incidence rates at the 4,000 Hz and 6,000 Hz frequencies were greater than double the rates at other frequencies. Octave band frequency results appeared approximately similar at all frequencies between exposure groups, but key differences were identified when researchers focused on the relative risks of sufficiently sized exposure groups.

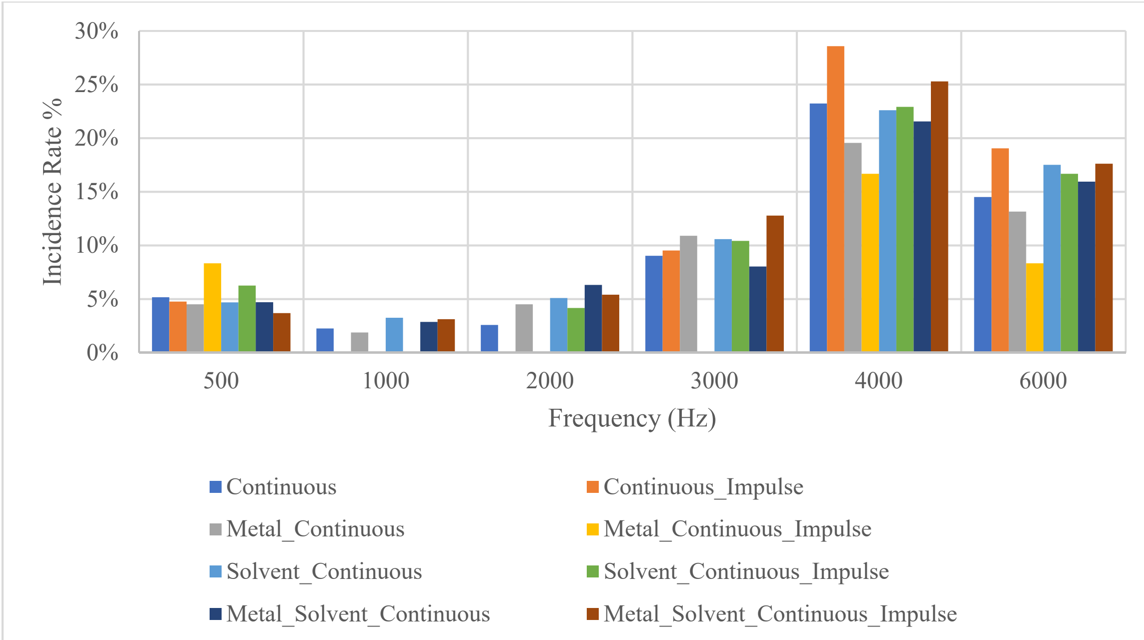

Figure 8. NIOSH STS Incidence Rate by Frequency for Left Ear

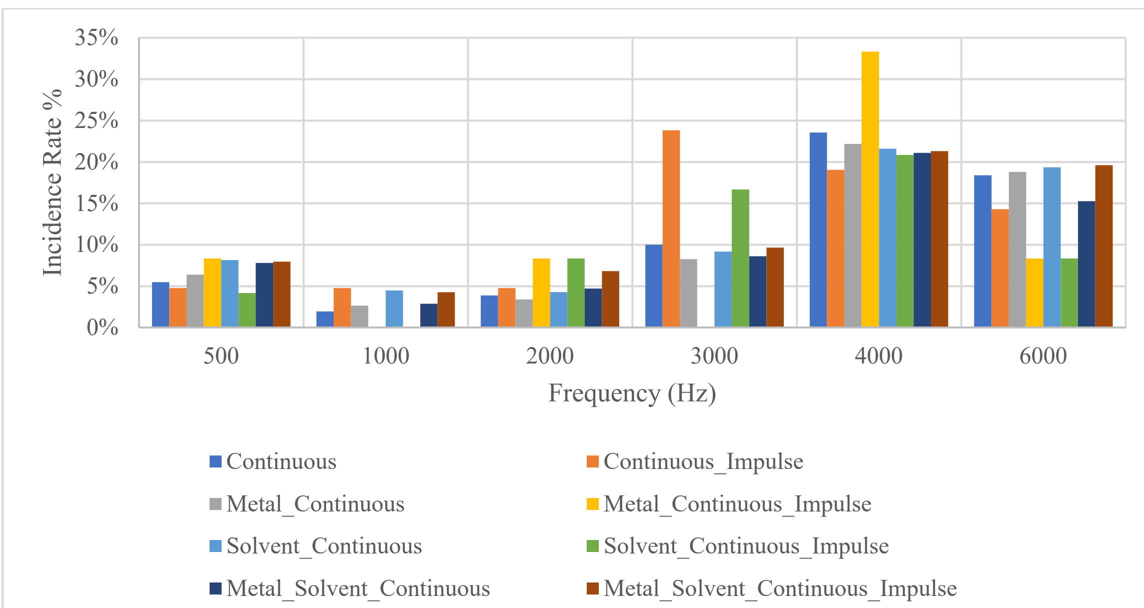

Figure 9. NIOSH STS Incidence Rate by Frequency for Right Ear

Researcher analysis of the relative risk of a NIOSH STS shift by independent frequency compared to the continuous noise only reference group identified potential ototoxic effects on hearing. An assessment of both the left ear (Table 19) and right ear (Table 20) identified a general trend of RR>1 at 1,000, 2,000, and 6,000 Hz frequencies. These combined effects were highest, RR>1.75, in the left ear at 2,000 Hz and the right ear at 1,000 and 2,000 Hz frequencies. The observed higher relative risks supported the researchers' postulation that ototoxic substances impacted frequencies outside those included in the DoD STS criterion and a potential source of the lower RR observed in the DoD STS model. Additionally, these results indicate continuous noise exposures as dominating hearing loss in the higher frequencies from 3,000 to 6,000 Hz, and ototoxic substances with concurrent noise exposure are dominating shifts at 1,000 and 2,000 Hz.

Table 19. Relative Risk of NIOSH STS in Left Ear by Frequency

Frequency (Hz)	500	1000	2000	3000	4000	6000
Continuous	Ref	Ref	Ref	Ref	Ref	Ref
Metal_Continuous	0.87	0.83	1.75	1.21	0.84	0.91
Solvent_Continuous	0.91	1.44	1.97	1.17	0.97	1.21
Metal_Solvent_Continuous	0.91	1.27	2.44	0.89	0.93	1.10
Metal_Solvent_Continuous_Impulse	0.72	1.38	2.09	1.42	1.09	1.21

Table 20. Relative Risk of NIOSH STS in Right Ear by Frequency

Frequency (Hz)	500	1000	2000	3000	4000	6000
Continuous	Ref	Ref	Ref	Ref	Ref	Ref
Metal_Continuous	1.17	1.36	0.87	0.83	0.94	1.02
Solvent_Continuous	1.49	2.32	1.10	0.92	0.92	1.05
Metal_Solvent_Continuous	1.42	1.48	1.21	0.86	0.90	0.83
Metal_Solvent_Continuous_Impulse	1.45	2.20	1.76	0.97	0.90	1.07

Researchers conducted further exploration with biostatistics confidence interval calculations of high RR frequencies to determine if there was a statistically significant difference between hearing changes in exposure groups compared to the continuous noise alone group. This assessment indicated combinations of noise with ototoxic substances yielded confidence intervals with no additional effects up to five times the relative risk of the NIOSH threshold shift (Table 21). In particular, the Metal/Solvent/Continuous exposure group demonstrated confidence (α=0.05) in RR ranging from 1.24 to 4.83 in the left ear at 2,000 Hz, thus supporting the observed lower frequency shifts from ototoxic substances identified by Chang et al. (2006). Additionally, researchers were able to observe increased effects from the impulse noise variable in the right ear but are unable to explain the etiology. Utilizing the Metal/Solvent/Continuous and continuous noise only reference groups' relative risk at 2,000 Hz in the left ear, a study power of ~63% was determined (Dane et al., 2011). Despite the evident combined effects, the specific contributions of ototoxic metal or solvents by assessing RR could not be determined due to the grouping methodology utilized in this study.

Table 21. Selected Relative Risk of NIOSH STS with Confidence Intervals

Left Ear at 2000 Hz			
SEG	RR	CI95L	CI95R
Metal_Continuous	1.75	0.75	4.05
Solvent_Continuous	1.97	0.94	4.13
Metal_Solvent_Continuous	2.44	1.24	4.83
Metal_Solvent_Continuous_Impulse	2.09	0.97	4.51
Right Ear at 1000 Hz			
SEG	RR	CI95L	CI95R
Metal_Continuous	1.36	0.48	3.82
Solvent_Continuous	2.32	1.00	5.34
Metal_Solvent_Continuous	1.48	0.65	3.38
Metal_Solvent_Continuous_Impulse	2.20	0.91	5.32
Right Ear at 2000 Hz			
SEG	RR	CI95L	CI95R
Metal_Continuous	0.87	0.38	1.99
Solvent_Continuous	1.10	0.57	2.15
Metal_Solvent_Continuous	1.21	0.67	2.21
Metal_Solvent_Continuous_Impulse	1.76	0.92	3.36

In summary, researchers implemented five definitions of hearing loss indicators to exposure group PTA data in order to determine the incidence rates of hearing loss and the relative risks compared to a continuous noise only reference group. Combinations of ototoxic substances appeared to have slight combined effects in almost all modeling, with the exception of the DoD STS model where effects were reduced to an RR<1. Researchers observed a maximum interaction, RR=1.57, with the Metal/Solvent/Continuous/Impulse exposure group utilizing the NIOSH material hearing impairment criteria, but with confidence intervals ranging from 0.83 to 2.97. Regardless of model definitions, the Solvent/Continuous and Metal/Solvent/Continuous/Impulse exposure groups predominantly displayed the most significant combined effects of all exposure group combinations. Utilizing the NIOSH STS method, researchers observed potentially ototoxic effects with lower confidence intervals approximately near a RR of 1.

Researchers further explored the NIOSH STS method by individual frequency and observed RRs>2 at 1,000 and 2,000 Hz frequencies. In particular, the Metal/Solvent/Continuous exposure group displayed the highest combined effects (RR=2.44 CI:1.24-4.83) in the left ear at 2000 Hz, indicating continuous noise is predominantly responsible for hearing changes at 3,000-6,000 Hz frequencies and apparent ototoxic effects in 1,000-2,000 Hz frequencies. Results indicate that the DoD STS method is not likely to observe the frequency shifts resultant from concomitant exposure to ototoxic substances and noise. Researchers concluded that the NIOSH STS method is a more sensitive evaluation criterion for identifying hearing loss that results from ototoxicants.

4.4 Exposure Group Descriptive Statistical Analysis by Frequency

Researchers utilized descriptive statistics to assess the average threshold shift at each PTA frequency. The average threshold shifts ranged from -1 dB HL to 8 dB HL for both the left (Figure 10) and right ear (Figure 11) across all frequencies. The characteristic noise notch observed in the NIOSH STS method was also observed in mean threshold shift values at 3,000, 4,000, and 6,000 Hz in both ears. The range of hearing thresholds between exposure groups at each frequency was slight, with values approximately within 2 dB HL for most exposure groups. Researchers postulated ototoxic effects on hearing loss were not clearly visible from 3,000 to 6,000 Hz due to the dominating effects of continuous noise exposure over ototoxic exposures found in animal studies (Carlson et al., 2018) and cross-sectional studies of human populations (Morata et al., 2011). As revealed in the NIOSH STS model, there was a larger difference in threshold shifts at 1,000 and 2,000 Hz for ototoxic exposures.

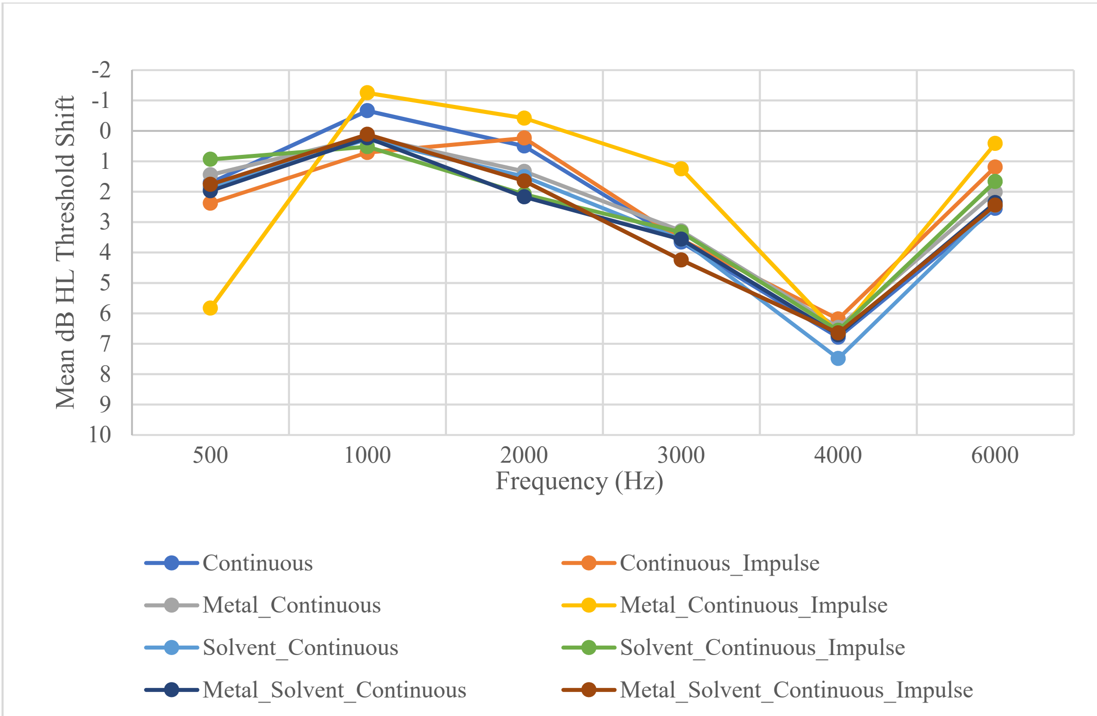

Figure 10. Mean Threshold Shifts by Frequency Left Ear

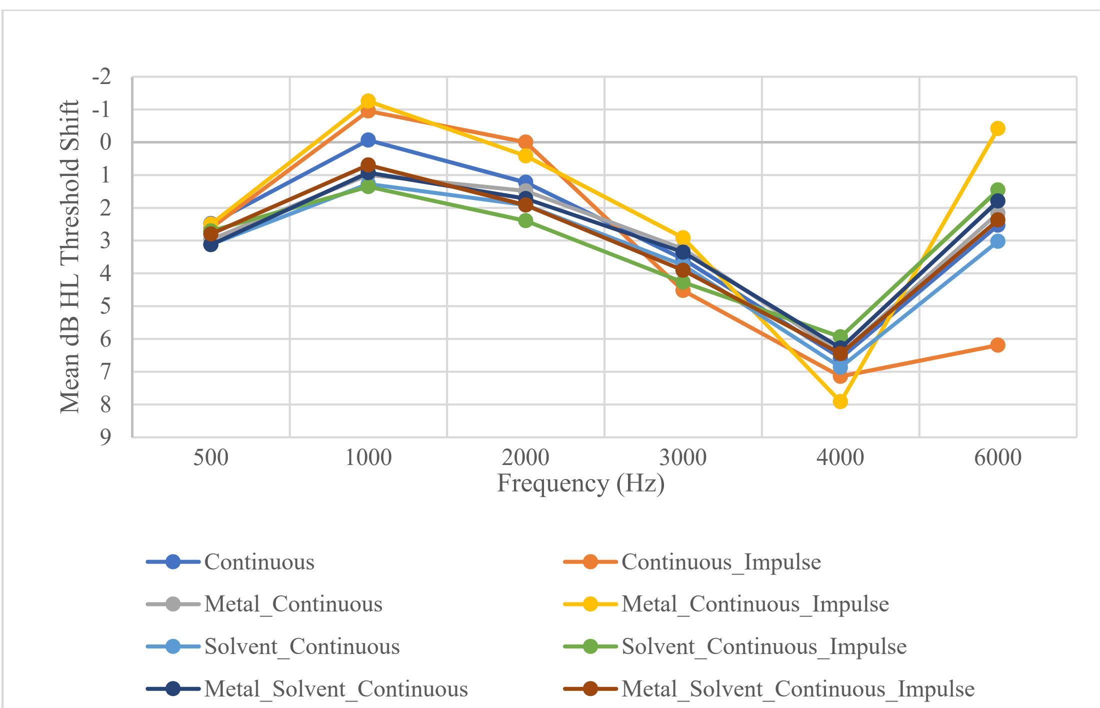

Figure 11. Mean Threshold Shifts by Frequency Right Ear

4.5 Exposure Group Inferential Statistical Analysis by Frequency

An objective of this research was the identification of significant differences between exposure groups at each frequency from 500 to 6,000 Hz. Prior to the selection of an inferential statistics method, researchers evaluated if exposure group data met the normal distribution criteria to conduct the one-way analysis of variance (ANOVA) test. Utilization of both the Shapiro-Wilk and Kolmogorov–Smirnov tests revealed the only normally distributed data was present in the smaller impulse noise exposure groups at certain frequencies. Based on this failure to meet the assumptions associated with one-way ANOVA, researchers initially conducted nonparametric comparison utilizing the Mann-Whitney U test for exploratory analysis of any significant differences, $\alpha=0.05$, between exposure groups with all frequency variables enumerated into one data field. The only near significant p-value (0.078) for the Mann-Whitney U test with enumerated frequency data was observed between the pairwise comparison of the Continuous and Solvent/Continuous exposure groups (Table 22). Researchers previously noted an RR>2 for the Solvent/Continuous exposure group in the right ear at 1,000 Hz utilizing the NIOSH STS method. Since this was an exploratory test limited by the shortfalls of enumerated data analysis, researchers did not apply p-value correction methods.

Table 22. Enumerated Value Mann-Whitney U for Exposure Groups Across All Frequencies

SEG	Comparison	p-value
Continuous	Continuous_Impulse	0.401
Continuous	Metal_Continuous	0.317
Continuous	Metal_Continuous_Impulse	0.152
Continuous	Solvent_Continuous	**0.078**
Continuous	Solvent_Continuous_Impulse	0.204
Continuous	Metal_Solvent_Continuous	0.281
Continuous	Metal_Solvent_Continuous_Impulse	0.473
Continuous_Impulse	Metal_Continuous	0.322
Continuous_Impulse	Metal_Continuous_Impulse	0.293
Continuous_Impulse	Solvent_Continuous	0.251
Continuous_Impulse	Solvent_Continuous_Impulse	0.238
Continuous_Impulse	Metal_Solvent_Continuous	0.333
Continuous_Impulse	Metal_Solvent_Continuous_Impulse	0.395
Metal_Continuous	Metal_Solvent_Continuous_Impulse	0.315
Metal_Continuous	Metal_Solvent_Continuous	0.495
Metal_Continuous	Metal_Continuous_Impulse	0.106
Metal_Continuous	Solvent_Continuous	0.19
Metal_Continuous	Solvent_Continuous_Impulse	0.289
Metal_Continuous_Impulse	Solvent_Continuous	0.08
Metal_Continuous_Impulse	Solvent_Continuous_Impulse	0.075
Metal_Continuous_Impulse	Metal_Solvent_Continuous	0.116
Metal_Continuous_Impulse	Metal_Solvent_Continuous_Impulse	0.167
Metal_Solvent_Continuous	Metal_Solvent_Continuous_Impulse	0.281
Solvent_Continuous	Solvent_Continuous_Impulse	0.455
Solvent_Continuous	Metal_Solvent_Continuous	0.13
Solvent_Continuous	Metal_Solvent_Continuous_Impulse	0.083
Solvent_Continuous_Impulse	Metal_Solvent_Continuous_Impulse	0.207
Solvent_Continuous_Impulse	Metal_Solvent_Continuous	0.281
*Bold denotes significant p-values, α=0.05		

Researchers further explored the differences between exposure groups by performing a Kruskal-Wallis non-parametric test to determine statistical differences between two or more groups. The observed p-values for the Kruskal-Wallis test ranged from 0.047 to 0.99, and the only significant difference, α=0.05, observed was in the left ear at the 2000 Hz frequency (Table 23). This potentially significant difference was previously noted as the only frequency and ear combination with definitive combined effects utilizing the NIOSH STS method.

Table 23. Kruskal-Wallis by Frequency

Ear	Frequency	p-value
Left	500	0.243
	1000	0.300
	2000	**0.047**
	3000	0.912
	4000	0.839
	6000	0.990
	Average 2,000 to 4,000 Hz	0.969
	Average 500 to 6,000 Hz	0.894
Right	500	0.938
	1000	0.199
	2000	0.753
	3000	0.963
	4000	0.933
	6000	0.524
	Average 2,000 to 4,000 Hz	0.869
	Average 500 to 6,000 Hz	0.673
*Bold denotes significant p-values, α=0.05		

Further exploration of the significant difference between exposure groups in the left ear at 2000 Hz was assessed utilizing a Mann-Whitney U post hoc pairwise test in Python. Researchers conducted the Mann-Whitney U test for unadjusted p-values, and Bonferroni corrected p-values. The Bonferroni adjustment is utilized to remove the potential for identifying significant errors by chance when conducting multiple statistical comparisons (Rosner, 1995). The Bonferroni adjustment utilized in this study is a product of the function of paired combinations of the eight study exposure groups equaling 28 possible pairs of groups. Python implementation of p-value adjustments for the Mann-Whitney U tests is conducted by multiplying the identified pairwise p-value by 28 to derive the adjusted p-value.

Researchers observed Mann-Whitney U test unadjusted p-values ranged from 0.001 to 0.972, and only one adjusted p-value with statistical significance (Table 24). The only significant pairwise comparison for both unadjusted p-values and adjusted p-values occurred between the comparison of continuous noise and Metal/Solvent/Continuous exposure groups. In this pairwise comparison, the Metal/Solvent/Continuous exposure group unadjusted p-value was 0.001, and the adjusted p-value was 0.023, implying significant differences compared to the continuous noise only group. The strength of this association was also noted previously in this study's evaluation of the NIOSH STS model. In comparison to literature, Schaal et al. (2018) observed a similar significant difference, p-value=0.007, in the left ear at 1000 Hz between High metals/High solvents/High noise and Low metals/Low solvents/High noise exposure groups. Researchers then sought to determine the potential causal factor for these differences between exposure groups at these frequencies.

Table 24. Mann-Whitney U for Left Ear at 2,000 Hz

Exposure Group	Exposure Group	p-value	p-value adjusted
Continuous	Continuous_Impulse	0.824	1
Continuous	Metal_Continuous	0.141	1
Continuous	Metal_Continuous_Impulse	0.570	1
Continuous	Metal_Solvent_Continuous	**0.001**	**0.023**
Continuous	Metal_Solvent_Continuous_Impulse	0.062	1
Continuous	Solvent_Continuous	0.088	1
Continuous	Solvent_Continuous_Impulse	0.093	1
Continuous_Impulse	Metal_Continuous	0.735	1
Metal_Continuous_Impulse	Continuous_Impulse	0.501	1
Metal_Continuous_Impulse	Metal_Continuous	0.302	1
Metal_Solvent_Continuous	Continuous_Impulse	0.394	1
Metal_Solvent_Continuous	Metal_Continuous	0.145	1
Metal_Solvent_Continuous	Metal_Continuous_Impulse	0.164	1
Metal_Solvent_Continuous_Impulse	Continuous_Impulse	0.661	1
Metal_Solvent_Continuous_Impulse	Metal_Continuous	0.790	1
Metal_Solvent_Continuous_Impulse	Metal_Continuous_Impulse	0.266	1
Metal_Solvent_Continuous_Impulse	Metal_Solvent_Continuous	0.204	1
Solvent_Continuous	Continuous_Impulse	0.706	1
Solvent_Continuous	Metal_Continuous	0.972	1
Solvent_Continuous	Metal_Continuous_Impulse	0.312	1
Solvent_Continuous	Metal_Solvent_Continuous	0.087	1
Solvent_Continuous	Metal_Solvent_Continuous_Impulse	0.779	1
Solvent_Continuous_Impulse	Continuous_Impulse	0.411	1
Solvent_Continuous_Impulse	Metal_Continuous	0.389	1
Solvent_Continuous_Impulse	Metal_Continuous_Impulse	0.148	1
Solvent_Continuous_Impulse	Metal_Solvent_Continuous	0.859	1
Solvent_Continuous_Impulse	Metal_Solvent_Continuous_Impulse	0.458	1
Solvent_Continuous_Impulse	Solvent_Continuous	0.388	1

Determining the causal factors associated with statistically significant differences between exposure groups is challenging due to limitations in this research methodology. Unable to determine magnitudes of exposure and limited by high-level exposure grouping, researchers reviewed descriptive statistical data in this study to pinpoint potential causal factors for differences. This analysis revealed the most likely significantly different exposure group, Metal/Solvent/Continuous, had an average continuous noise exposure duration of 7.8 years, and the reference group, continuous noise only, averaged 6.1 years. Therefore, it is likely the significant results from the

Mann-Whitney U test are associated with the 28% difference between the years of exposure to continuous noise.

4.6 Logistic Regression

A limited logistic regression model was built to determine the variables with significant impacts on the outcome of hearing loss changes. Researchers selected the dependent variable of a NIOSH STS as the outcome of interest in the logistic regression model due to the smaller range of confidence intervals, and the observed higher RR between exposure groups and the continuous noise reference group. Researchers structured the dependent variable with a binary outcome, 1 for the presence of NIOSH STS and 0 for lack of a NIOSH STS. Independent variables included:

- Age
- Sex- binary variable. Male=1 and Female=0
- Audiotime- duration in years between baseline and final audiogram.
- Continuous- exposure duration in years to continuous noise.
- Solvent- exposure duration in years to ototoxic solvents.
- Metal- exposure duration in years to ototoxic metals.
- Impulse- exposure duration in years to impulse noise.
- MetalCount- the maximum number of unique ototoxic metals an individual was exposed during employment.
- SolventCount- the maximum number of unique ototoxic solvents an individual was exposed during employment.

The results of the logistic regression demonstrated a low R-squared value (0.045) and independent variable p-values ranging from 0.000 to 0.909 (Figure 12). The independent variables that uniquely contributed to developing a NIOSH STS (α=0.05) while controlling for the effects of all other variables included Age, Sex, Audiotime, and Continuous variables. Researchers determined these variables were in alignment with those expected to influence observed NIHL rates from occupational exposures. Researchers assumed the Sex variable was likely only a significant factor due to the predominately male population (88%) in this study. Although this is a basic regression model, results support the previous conclusion that significant differences in non-parametric tests are potentially a result of differences from exposure to continuous noise hazards. Comparison of Python statistics results to JMP (SAS Institute Inc., Cary, North Carolina) validated results were approximately similar between programs and sufficient for this research and further exploratory DoD research modeling.

```
==============================================================================
Dep. Variable:             NIOSHShift   No. Observations:                 2372
Model:                          Logit   Df Residuals:                     2362
Method:                           MLE   Df Model:                            9
Date:                Tue, 07 Jan 2020   Pseudo R-squ.:                 0.04516
Time:                        10:01:07   Log-Likelihood:                -1544.0
converged:                       True   LL-Null:                       -1617.0
                                        LLR p-value:                 5.841e-27
================================================================================
                  coef    std err          z      P>|z|      [0.025      0.975]
--------------------------------------------------------------------------------
Intercept      -2.5466      0.265     -9.610      0.000      -3.066      -2.027
Age             0.0378      0.005      8.382      0.000       0.029       0.047
Sex             0.4229      0.133      3.168      0.002       0.161       0.685
Audiotime       0.0514      0.019      2.709      0.007       0.014       0.089
Continuous      0.0447      0.023      1.977      0.048       0.000       0.089
Solvent         0.0019      0.016      0.114      0.909      -0.030       0.034
Metal          -0.0254      0.018     -1.414      0.157      -0.061       0.010
Impact         -0.0035      0.018     -0.193      0.847      -0.039       0.032
MetalCount      0.0785      0.053      1.489      0.137      -0.025       0.182
SolventCount    0.0152      0.035      0.436      0.663      -0.053       0.084
================================================================================
```

Figure 12. Logistic Regression for NIOSH Significant Threshold Shift

4.7 Conclusion

Researchers implemented multiple data analysis approaches to validate the research model's processing of audiometric data from DOEHRS-HC, determine potentially significant factors in hearing loss, and identify the optimal PTA evaluation criteria for evaluating the hearing effects of ototoxic substances. Utilizing DoD STS and OSHA adjusted incidence rate data, researchers validated this study's audiometric selection criteria were comparable to published data for similar time frames. After extensive analysis of multiple methods of detecting hearing change, researchers identified the NIOSH STS method as the most sensitive PTA evaluation criteria capable of detecting potential combined effects for all ototoxic exposure combinations.

NIOSH STS model effects are likely the result of the inclusion of the 500, 1,000, and 6,000 Hz frequencies and independent frequency analysis vice averaging functions utilized in the STS method. With the NIOSH STS method, a general trend of combined ototoxic impacts at 1,000 and 2,000 Hz was observed in both ears, and a significant increase in risk (RR=2.44 CI 1.24-4.83) occurred in the left ear at 2,000 Hz for the Metal/Solvent/Continuous exposure. Further descriptive and inferential statistical analysis confirmed there is likely a significant effect (Bonferroni adjusted p-value=0.023) on hearing threshold shifts in the left ear at 2,000 Hz for individuals grouped by Metal/Solvent/Continuous exposure.

Researchers then conducted a logistic regression determining the significant factors in the development of a NIOSH STS shift were age, sex, the duration between audiograms, and the duration of exposure to continuous noise. The significant variables in the regression model could explain the statistical differences in the left ear at 2,000 Hz, and descriptive analysis indicated a longer duration of exposure to continuous noise for the Metal/Solvent/Continuous exposure group compared to the continuous noise only reference group. Based on the grouping and lack of exposure values in this study, further evaluation of strengths of association could not be performed.

V. Conclusion

5.1 Chapter Overview

The focus of this chapter is the discussion of research conclusions, limitations, recommendations for action, and future research opportunities. Research conclusions are synthesized to frame results, limitations, and future actions. In the assessment of results, the limitations of this research are discussed as a product of the quality, processing, and availability of data. These limitations could be reduced through future actions focused on the enhancement of DOEHRS-IH data, refinement of DoD ototoxic guidance, and the expansion of the HCP program. Finally, discussion of potential future research opportunities includes the refinement of the utilized research model, expansion of the study population, and the creation of a more extensive audiogram evaluation methodology.

5.2 Research Conclusions

Researchers identified combinations of ototoxic substances appeared to have slight combined effects in almost all modeling, with the exception of the DoD STS model where effects were reduced to an $RR<1$. The maximum observed interaction observed across all PTA evaluation models was the Metal/Solvent/Continuous/Impulse exposure group ($RR=1.57$) utilizing the NIOSH material hearing impairment criteria, but without enough confidence in combined effects (CI 0.83-2.97). These broad ranges of confidence are primarily a product of the small size of the study population and the low rates of hearing loss development. Additionally, researchers sought to utilize impulse noise as an exposure group variable, but group sizes with this combination were not large enough for analysis.

Overall, the Solvent/Continuous and Metal/Solvent/Continuous/Impulse exposure groups consistently displayed the most significant combined effects of all exposure group combinations. In assessing PTA criteria, researchers observed potentially ototoxic effects for all ototoxic exposure combinations utilizing the NIOSH STS method. Further exploration of the NIOSH STS method by individual frequency found the relative risk for some ototoxic exposure groups was more than double the reference group at 1,000 and 2,000 Hz frequencies. In particular, the Metal/Solvent/Continuous exposure group displayed the highest combined effects (RR=2.44 CI:1.24-4.83) in the left ear at 2,000 Hz. These results indicate that continuous noise exposure may dominate higher frequencies, and therefore the combined effects of concomitant exposure to ototoxic substances to continuous noise are only noticeable at lower frequencies.

Descriptive statistical analysis of the average threshold shifts was approximately similar, and the characteristic noise notch was observed at 3,000, 4,000, and 6,000 Hz in both ears. The range of hearing loss between exposure groups at each frequency was slight, with values approximately within 2 dB HL for most exposure groups. Researchers again postulated ototoxic effects on hearing loss were not clearly visible from 3,000 to 6,000 Hz due to the dominating effects of continuous noise exposure over ototoxic exposures. As noticed in the NIOSH STS model, broader mean threshold shifts were observed at 1,000 and 2,000 Hz for ototoxic exposure groups. Inferential statistical analysis with Mann-Whitney U tests confirmed the Metal/Solvent/Continuous exposure group unadjusted p-value was 0.001, and the adjusted p-value was 0.023, as significantly different than the continuous noise only reference group and in agreement with NIOSH STS relative risk calculations.

Logistic regression was conducted to determine which characteristics best predict the development of a NIOSH STS while controlling for the confounding effects of the other variables. Another analysis of descriptive data indicated that the Metal/Solvent/Continuous exposure group had an average of 28% higher duration of exposure to continuous noise. Therefore, the observed significance of the Metal/Solvent/Continuous exposure group could be a result of longer duration exposure to noise and the lack of significance of ototoxic substances in logistic regression. Future studies should focus on expanding the study population or revaluation of exposure grouping criteria by exposure levels.

In conclusion, researchers established there are likely hearing loss effects from exposure to ototoxic substances at the 1,000 and 2,000 Hz frequencies. Without detailed statistical analysis, it appears the NISOH STS evaluation method is the most sensitive in observing these changes through the inclusion of all frequencies from 500 to 6,000 Hz and a lack of averaging functions. This research identified that the adopted audiometric record processing methods closely matched published rates in literature and provided a simple method for analysis of large volumes of data.

5.3 Limitations

Data quality, processing, and availability limit the power of observed potential casual relationships and statistical inferences in this research. Researchers assumed that the current DoD exposure assessment strategy, a process that maximizes limited resources to manage prioritized risks, sufficiently captured the actual exposure hazards in an occupational setting. Researchers were unable to conduct independent basic characterization or exposure assessment by sampling, and therefore a foundational limitation to this study is assuming DOEHRS-IH SEG data is of sufficient quality for research. An ototoxic substance with an incorrectly entered Chemical Abstracts Service (CAS) registry number to a similar derivative would prevent inclusion in this research. Additionally, SEGs form the foundation of the exposure assessment strategy, and the incorrect assignment of individuals to SEGs via the "Workplace Personnel Roster" report can significantly alter the exposures assigned to an individual. The principal data quality limitation encountered in this research was the lack of measured chemical concentration and measured noise levels for all assessed hazards in the "Analyze Occupational Exposure Hazards" report. This information gap required researchers to deviate from the intention to create hazard-specific time-weighted averages and, instead, required the creation of dichotomous exposure variables based on an estimated duration of exposure.

The lack of integration between DOEHRS-IH and DOEHRS-HC generated numerous study limitations during the execution of data processing by researchers. Researchers utilized selected baseline audiogram and final audiogram records from DOEHRS-HC data to "fence" SEG exposures and disregard SEG assignments outside the selected period. In this process, individuals may have ototoxic exposures that only occurred before the study time frame and not within the study time frame potentially leading to a study classification of continuous noise only exposure. While researchers screened individuals to ensure they possessed normal hearing at the selected baseline audiogram, there is a possibility that individuals had significant chronic ototoxic exposures that occurred before their respective “fenced” period. This limitation could overestimate the size of the continuous noise only exposure group identified in this research.

A challenge encountered during the processing of data was an individual’s assignment to overlapping unique SEGs. Researchers were unable to differentiate which SEGs dominated an individual's work schedule and were unable to determine a balanced approach to estimating actual exposures. The methodology in this research considered all SEG assignments equal in magnitude, and researchers adopted a cumulative approach to estimate the duration of exposure to a substance regardless of date overlaps. This approach is likely to overestimate the exposure durations for these individuals. Additionally, researchers derived an individual’s overall count of exposure to unique ototoxic substances by calculating the maximum quantity of substances within unique SEG assignments regardless of duration. This max count approach could potentially represent the shortest duration SEG assignment and not the average quantity of substances in a worker’s occupational history.

Data availability limited the removal of confounding factors, establishment of reference baseline audiograms for all individuals, and the verification of medical diagnosis of impaired hearing. The only demographic data available for researchers in this study were age and gender. Therefore, this research was unable to account for confounding factors of hearing loss that could include personal usage of firearms, high noise and high ototoxicant recreational activities, smoking, alcohol usage, or ototoxic pharmaceutical usage. Each of these factors could be significant contributors to the indicators of hearing loss observed in the study. DOEHRS-HC audiometric data collection covered 2005 to 2019, and researchers observed this timeframe did not capture each individual's reference audiogram with the description “prior to initial duty in noise.” Researcher establishment of baseline records utilizing the annual audiogram type designation may not reflect the values present in the unavailable reference audiogram records. Additionally, it is essential to note that DOEHRS-HC data does not include a verified medical diagnosis of hearing impairment. The lack of availability of medical records prevented researchers from validating hearing impairment, and thus this research relies only on changes in hearing over time. Lastly, the DOEHRS-HC records collected from 2005-2019 totaled approximately 33,000 individuals, while the DOEHRS-IH records for the same time period totaled approximately 20,000 individuals. This only allowed for an analysis of 60% of individuals with audiometric records indicating a substantial portion of the worker population is not captured in DOEHRS-IH. Further study limitations are characterized in Table 25 by assumption and their respective direction of risk over or underestimation.

Table 25. Risk Uncertainty Table

Assumption	Potential Direction of Risk Estimation
Equal ototoxicity weight of evidence for all metals and solvents	+
Utilization of non-reference audiograms for threshold calculations	+/-
Final audiogram matching threshold of 7 days vice 30 days	+/-
Inclusion of audiograms with unknown ENT status	+/-
Baseline audiograms thresholds <=25 dB HL	+/-
Utilization of three-year duration of exposure to ototoxic substances	-
Dichotomous exposure variables	+
SEG "fencing" procedure	-
Aggregation of SEG assignments with equal weight	+
Incorrect assignment of individuals to SEGs in workplace assignment	+
Keyword classification of impulse noise sources	+/-
Inability to conduct independent verification of exposure assessments	+/-
All SEG exposure assessments apply to all individuals assigned to SEG regardless of dates	+
Unable to identify confounding factors via personnel surveys	+
Lack of a medical diagnosis of hearing loss	+
Lack of DOEHRS-IH assignments for the number of unique individuals identified in DOEHRS-HC during the same time frame	+/-
+ Overestimation of Risk - Underestimation of Risk	

5.4 Recommendations for Action

The DoD could potentially increase the power of future ototoxic epidemiology studies through the enhancement of DOEHRS-IH data, refinement of DoD ototoxic guidance, and the expansion of the HCP program. DOEHRS-IH could be enhanced by the complete usage of the existing DEOHRS-IH report "Analyze Occupational Exposure Hazards." As previously described, the installation assessed in this research lacked complete exposure value data in this report, which limited the ability to create time-weighted average exposures for ototoxic and noise hazards. The USAF could implement a service level policy requiring base industrial hygiene program offices to adopt an exposure assessment process that assigns an interim exposure value for each hazard that cannot be immediately modeled or sampled. These interim values could adopt the AIHA SEG exposure control category paradigm that classifies hazards in stratified groups according to specific percentages of OEL (AIHA, 2015). This policy change would be a low impact on the DoD and enable the potential establishment of dose-response relationships in future studies. Regarding impulse noise exposures, program offices should validate "Installation Noise Sample Log" reports to ensure properly documented "impulse/impact" noise types. These recommendations would still require the same extensive data analysis conducted in this study, and further institutional actions would be needed to gain efficiencies in post-collection data analysis.

Increasing the efficiency and repeatability of ototoxic research would necessitate the refinement of DoD ototoxic guidance to specific substances and would provide a standard ototoxic evaluation report for each branch of the armed services. As previously discussed, current DoD guidance directs the evaluation of ototoxic substances but does not illuminate specific substances or exposure levels of concern. Given the litany of potentially ototoxic substances and uncertainty regarding the severity of their ototoxic effects, this nonspecific guidance can lead to variations between research efforts and difficulty in comparing the effects of exposure. Therefore, the DoD should focus efforts by clearly defining ototoxic substances of concern to prevent the inclusion of questionable ototoxins. As identified in this research, the NIOSH STS method is likely to demonstrate an increased relative risk of hearing changes from exposures to ototoxic substances. A DoD policy requiring the usage of the NIOSH STS method in future assessment of existing data for ototoxic effects would further illuminate its applicability in determining significantly different threshold shifts between combinations of exposure groups. The implementation of NIOSH STS criteria would be a minor and low-cost change to information processing systems.

Regardless of the establishment of a DoD specific ototoxic substance list, DOEHRS-IH system owners should create a standard report template or “flag” method for ototoxic substances to increase data collection efficiency and reduce variation. As identified in this methodology, the current approach requires searching by keyword or CAS registry number. Automation of this process through a database query that filters exposures based on identified ototoxins would provide a quick, repeatable approach to exposure group identification and data collection. These DoD level approaches would require more effort compared to the usage of existing reports but could significantly increase the efficiency of future studies. However, the major limitation of audiometric record availability limited to HCP assigned personnel still exists.

A comprehensive evaluation of ototoxic exposure by the DoD will require the expansion of the HCP to include either individuals with ototoxic substance only exposures or all individuals regardless of exposure. Currently, the audiometric data available for epidemiology studies is only a reflection of SEGs assessed as exposed to continuous noise levels greater than an 85 dBA TWA. This designation limits the comparison of exposure groups with a potential for hearing loss due to ototoxic substances only. Additionally, the lack of audiometric data available for potentially non-noise exposed individuals prevents the comparison of data to an actual non-exposed reference population. While the expansion of the HCP may enable understanding of hearing loss from ototoxic only exposures and provide a better reference population, there are likely to be significant costs incurred in the audiometric evaluation program. These recommendations for action vary from simple changes to service level policy to the significant expansion of current HCP efforts but given the VA documented prevalence of hearing-related disease, they are likely cost-effective alternatives to disability payments.

5.5 Recommendations for Future Research

Future research could build upon this study through the refinement of the utilized research model, expansion of the study population, and the creation of a more extensive audiogram evaluation methodology. Assuming DOEHRS-IH data at other installations is of similar quality to that identified in this study, future research could refine the utilized model to focus on developing time-weighted averages with available data in the "Analyze Occupational Exposure Hazards" report. This approach would provide future researchers with the ability to group personnel according to high/low exposure group combinations and evaluate the significance of exposure levels in regression models. However, if incomplete quantitative exposure levels are identified in other populations, similar to what was identified in this research, underestimation of actual exposures is expected to continue. Another approach to the refinement of this research model would be the initiation of a service level "data call" for ototoxic exposures to industrial hygiene program offices. Large volume data analysis can potentially fail to incorporate the subject matter expertise of local IH professionals and aggregation of locally evaluated data.

Expansion of the study population could potentially decrease the relative risk confidence intervals found in this study by increasing the number of individuals with hearing changes. Researchers recommend this expansion include all Air Force Material Command depots with similar civilian employee occupational codes to provide researchers with the ability to compare potentially identical SEGs between installations. This comparison could either allow researchers to fill gaps in exposure assessments or establish study exposure groups based on similar work processes. Researchers continue to recommend the exclusion of military personnel due to unique military exposures and temporary installation assignments that would reduce exposure duration to noise and ototoxicants. This expansion could enable a more extensive and stringent analysis of audiometric data.

The final recommendation for future research is the creation of a comprehensive DOEHRS-HC threshold shift calculation model. This research methodology was limited to the usage of a first and last audiogram method due to the experience of the programmer, time constraints, and the size of the study population. Future models should seek to calculate threshold shifts for each succeeding audiogram record from a selected baseline record, thus enabling researchers to identify temporal effects of varying degrees of exposure. If the study population is expanded, researchers may be able to utilize a reference audiogram with a "prior to initial duty in noise" description for all baseline records and still maintain a sufficient sample size for exposure groups.

Bibliography

ACGIH. (2019). *TLVs and BEIs: Threshold limit values for chemical substances and physical agents biological exposure indices*. American Conference of Governmental Industrial Hygienists.

AIHA. (2015). *A Strategy for Assessing and Managing Occupational Exposures* (4th ed). American Industrial Hygiene Association.

Ackley, R. S., Decker, T.N, & Limb, C.J. (2007). *An essential guide to hearing and balance disorders*. Lawrence Erlbaum Associates.

Amrein, B. E., & Letowski, T. R. (2012). *High-Level Impulse Sounds and Human Hearing: Standards, Physiology, Quantification* (ARL-TR-6017). Army Research Laboratory. https://www.arl.army.mil/arlreports/2012/ARL-TR-6017.pdf

Berne, R.M., & Levy, M.N. (1998). *Physiology* (4th ed). Mosby.

Bruce, R.D, Bommer, A.S., Mortiz, C.T., Lefkowitz, K.A., & Hart, N.W. (2011) Anna, D.H. (Ed.), *The occupational environment: its evaluation, control, and management* (3rd ed). American Industrial Hygiene Association.

Campo, P., Maguin, K., Gabriel, S., Moller, A., Dolores, M., & Toppila, E. (2009). *Combined exposure to noise and ototoxic substances*. European Agency for Safety and Health at Work. https://doi.org/10.2802/16028

Carlson, K., & Neitzel, R. L. (2019). Hearing loss, lead (Pb) exposure, and noise: a sound approach to ototoxicity exploration. *Journal of Toxicology and Environmental Health, Part B*, *21*(5), 335–355. https://doi.org/10.1080/10937404.2018.1562391

Carlson, K., Schacht, J., & Neitzel, R. L. (2018). Assessing ototoxicity due to chronic lead and cadmium intake with and without noise exposure in the mature mouse. *Journal of Toxicology and Environmental Health, Part A*, *81*(20), 1041–1057. https://doi.org/10.1080/15287394.2018.1521320

Carreres Pons, M., Chalansonnet, M., Venet, T., Thomas, A., Nunge, H., Merlen, L., Campo, P. (2017). Carbon disulfide potentiates the effects of impulse noise on the organ of Corti. *Neurotoxicology*, *59*, 79–87. https://doi.org/10.1016/j.neuro.2017.02.003

CDC. (2016). Hearing impairment among noise-exposed workers united states. *Morbidity and Mortality Weekly Report, 65*(15). https://doi.org/10.1002/ajim.22565/epdf

Chang, S., Chen, C., Lien, C., & Sung, F. (2006). Hearing loss in workers exposed to toluene and noise. *Environmental Health Perspectives, 114*(8), 1283–1286. https://doi.org/10.1289/ehp.8959

Choi, Y., & Park, S. K. (2017). Environmental exposures to lead, mercury, and cadmium and hearing loss in adults and adolescents: KHANES 2010-2012. *Environmental Health Perspectives, 125*(6). https://doi.org/10.1289/EHP565

Coles, R.A., Garinther, G.R., Hodge, D.C., Rice, C.G. (1968). Hazardous exposure to impulse noise. *The Journal of the Acoustical Society of America*, *43*(336). https://doi: 10.1121/1.1910785

Crofton, K. M., Lassiter, T. L., & Rebert, C. S. (1994). Solvent-induced ototoxicity in rats: An atypical selective mid-frequency hearing deficit. *Hearing Research*, *80*(1), 25–30. https://doi.org/10.1016/0378-5955(94)90005-1

Davis, R. R., & Clavier, O. (2017). Impulsive noise: A brief review. *Hearing Research*, *349*, 34–36. https://doi.org/10.1016/j.heares.2016.10.020

Dean A.G., Arner, T.G., Sunki, G.G., Friedman, R., Lantinga, M., Sangam, S., Zubieta, J.C., Sullivan, K.M., Brendel, K.A., Gao, Z., Fontaine, N., Shu, M., Fuller, G., Smith, D.C., Nitschke, D.A., & Fagan, R.F. (2011) *Epi Info, a database and statistics program for public health professionals*. CDC.

Dement, J., Welch, L. S., Ringen, K., Cranford, K., & Quinn, P. (2018). Hearing loss among older construction workers: Updated analyses. *American Journal of Industrial Medicine*, *61*(4), 326–335. https://doi.org/10.1002/ajim.22827

Defense Health Agency. (2018). *DOEHRS-IH* [Fact sheet]. Retrieved from https://www.health.mil/Reference-Center/Fact-Sheets/2019/04/05/DOEHRS-IH

Defense Health Agency. (2019). *DOEHRS-HC* [Fact sheet]. Retrieved from https://health.mil/Reference-Center/Fact-Sheets/2019/06/17/DOEHRS-HC

Department of Defense. (2019). *Hearing Conservation Program* (DoD Instruction 6055.12) https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodi/605512p.pdf?ver=2019-08-14-073309-537

Department of Defense. (2015). *Standard Noise Limits* (MIL-STD-1474E). https://www.arl.army.mil/wp-content/uploads/2019/12/ahaah-MIL-STD-1474E-Final-15Apr2015.pdf

Department of Veterans Affairs. (2018). *Veterans Benefits Administration Annual Benefits Report Fiscal Year 2017*. https://www.benefits.va.gov/REPORTS/abr/docs/2017_abr.pdf

Department of Veterans Affairs. (2019). *Veterans Benefits Administration Annual Benefits Report Fiscal Year 2018*. https://www.benefits.va.gov/REPORTS/abr/docs/2018-abr.pdf

Fuente, A., Qiu, W., Zhang, M., Xie, H., Kardous, C. A., Campo, P., Morata, T. (2018). 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. *The Journal of the Acoustical Society of America (143)*1704. https://doi.org/10.1121/1.5028368

Gelfand, S. A. (2004). *Hearing: An introduction to psychological and physiological acoustics* (4th ed). Marcel Dekker.

Gordis, L. (2014). *Epidemiology* (5th ed). Elsevier Saunders.

Guinan, J. J. (2018). Olivocochlear efferents: Their action, effects, measurement and uses, and the impact of the new conception of cochlear mechanical responses. *Hearing Research*, *362*, 38–47. https://doi.org/10.1016/j.heares.2017.12.012

Henderson, D., Bielefeld, E. C., Harris, K. C., & Hu, B. H. (2006). The role of oxidative stress in noise-induced hearing loss. *Ear and Hearing*, *27*(1), 1-19. https://doi: 10.1097/01.aud.0000191942. 36672.f3

Hormozi, M., Ansari-Moghaddam, A., Mirzaei, R., Dehghan Haghighi, J., & Eftekharian, F. (2017). The risk of hearing loss associated with occupational exposure to organic solvents mixture with and without concurrent noise exposure: A systematic review and meta-analysis. *International Journal of Occupational Medicine and Environmental Health*, *30*(4), 521–535. https://doi.org/10.13075/ijomeh.1896.01024

Hu, B. H., Henderson, D., & Nicotera, T. M. (2006). Extremely rapid induction of outer hair cell apoptosis in the chinchilla cochlea following exposure to impulse noise. *Hearing Research, 211(1)*, 16–25. https://doi.org/10.1016/j.heares.2005.08.006

Humes, L.E, Joellenbeck, L.M., Durch, J.S. (2006). *Noise and Military Service: Implications for Hearing Loss and Tinnitus*. The National Academies Press. https://doi.org/10.17226/11443.

Johnson, A.C., & Morata, T. C. (2010). Occupational exposure to chemicals and hearing impairment. *Arbete och Halsa, 44*(142), 1-177. Retrieved from https://gupea.ub.gu.se/handle/2077/23240

Jones, H. G., Greene, N. T., & Ahroon, W. A. (2018). Human middle-ear muscles rarely contract in anticipation of acoustic impulses: Implications for hearing risk assessments. *Hearing Research, 378,* 53-62. https://doi.org/10.1016/J.HEARES.2018.11.006

Juárez-Pérez, C. A., Torres-Valenzuela, A., Haro-García, L. C., Borja-Aburto, V. H., & Aguilar-Madrid, G. (2014). Ototoxicity effects of low exposure to solvent mixture among paint manufacturing workers. *International Journal of Audiology*, *53*(6), 370–376. https://doi.org/10.3109/14992027.2014.888597

Kaufman, L. R., Lemasters, G. K., Olsen, D. M., & Succop, P. (2005). Effects of concurrent noise and jet fuel exposure on hearing loss. *Journal of Occupational and Environmental Medicine, 47*(3), 212-218. https://doi.org/10.1097/01.jom.0000155710.28289.0e

Lewkowski, K., Heyworth, J. S., Li, I. W., Williams, W., Mccausland, K., Gray, C., Fritschi, L. (2019). Exposure to noise and ototoxic chemicals in the Australian workforce. *Occupational and Environmental Medicine, 76,* 341–348. https://doi.org/10.1136/oemed-2018-105471

Lilienfeld, D. E., Stolley, P.D. (1994). *Foundations of Epidemiology* (3rd ed). Oxford University Press.

Lund, S. P., & Kristiansen, G. B. (2008). Hazards to hearing from combined exposure to toluene and noise in rats. *International Journal of Occupational Medicine and Environmental Health*, *21*(1), 47–57. https://doi.org/10.2478/v10001-008-0008-x

Masterson, E. A., Tak, Ã. S., Themann, C. L., Wall, D. K., Groenewold, M. R., Deddens, J. A., & Calvert, G. M. (2013). Prevalence of hearing loss in the united states by industry. *American Journal of Industrial Medicine, 56*(6), 670–681. https://doi.org/10.1002/ajim.22082

Masterson, E. A., & Sweeney, M. H. (2014). Prevalence of workers with shifts in hearing by industry: A comparison of OSHA and NIOSH hearing shift criteria. *Journal of Occupational and Environmental Medicine*, *56*(4), 446–455. https://doi.org/10.1097/JOM.0000000000000124

Masterson, E. A., & Deddens, J. A. (2015). Trends in worker hearing loss by industry sector, 1981–2010. *American Journal of Industrial Medicine, 58*(4), 392–401. https://doi.org/10.1002/ajim.22429

McKenna, E. A., & Williams, D. A. (2018). *United States Air Force Hearing Conservation Program, Annual Report for Calendar Year 2016* (AFRL-SA-WP-SR-2018-0005). AFRL. https://apps.dtic.mil/dtic/tr/fulltext/u2/1052693.pdf

Metwally, F. M., Aziz, H. M., Mahdy-Abdallah, H., Elgelil, K.S.A., & El-Tahlawy, E.M. (2012). Effect of combined occupational exposure to noise and organic solvents on hearing. *Toxicology and Industrial Health, 28*(10), 901-907. https://doi.org/10.1177/0748233711427051

Moore, B. C. (2003). *An Introduction to the Psychology of Hearing* (5th ed). Academic Press.

Morata, T. C., Dunn, D. E., & Sieber, W. K. (1994). Occupational exposure to noise and ototoxic organic solvents. *Archives of Environmental Health*, *49*(5), 359–365. https://doi.org/10.1080/00039896.1994.9954988

Morata, T. C., Sliwinska-Kowalska, M., Johnson, A. C., Starck, J., Pawlas, K., Zamyslowska-Szmytke, E., Prasher, D. (2011). A multicenter study on the audiometric findings of styrene-exposed workers. *International Journal of Audiology*, *50*(10), 652–660. https://doi.org/10.3109/14992027.2011.588965

NIOSH. (1998). *Occupational Noise Exposure*. National Institute for Occupational Health and Safety. https://www.cdc.gov/niosh/docs/98-126/pdfs/98-126.pdf?id=10.26616/NIOSHPUB98126

OSHA. (2018). *Preventing Hearing Loss Caused by Chemical (Ototoxicity) and Noise Exposure* (DHHS NIOSH Publication Number 2018-124). https://www.cdc.gov/niosh/docs/2018-124/pdfs/2018-124.pdf?id=10.26616/NIOSHPUB2018124

Rabinowtiz, P. Cantley, L.F, Galusha, D., Trufan, S., Swersey, D., Dixon-Ernst, C., Ramierz, V., Neitzel, R. (2018). Assessing hearing conservation program effectiveness: Results of a multisite assessment. *Journal of Occupational & Environmental Medicine*, *60*(1), 29–35. https://doi-org.afit.idm.oclc.org/10.1097/JOM.0000000000001125

Rice, C. G., & Martin, A. M. (1973). Impulse noise damage risk criteria. *Journal of Sound and Vibration*, *28*(3), 359–367. https://doi.org/10.1016/S0022-460X(73)80030-6

Roeser, R. J., Valenete, M., & Hosford-Dunn, H. (2000). *Audiology Diagnosis*. Thieme.

Rosner, B. (1995*). Fundamentals of Biostatistics* (4th ed). Duxbury Press.

Roth, J. A., & Salvi, R. (2016). Ototoxicity of Divalent Metals. *Neurotoxicity Research*, *30*(2), 268–282. https://doi.org/10.1007/s12640-016-9627-3

Sataloff, R.T., Sataloff, J. (2006). *Occupational Hearing Loss.* CRC Press.

Schaal, N. C., Slagley, J. M., Richburg, C. M. C., Zreiqat, M. M., & Paschold, H. W. (2018). Chemical-induced hearing loss in shipyard workers. *Journal of Occupational and Environmental Medicine*, *60*(1), 55–62. https://doi.org/10.1097/JOM.0000000000001186

Sliwinska-Kowalska, M., Zamyslowska-Szymtke, E., Szymczak, W., Kotylo, P., Fiszer, M., Dudarewicz, A., Stolarek, R. (2001). Hearing loss among workers exposed to moderate concentrations of solvents. *Scandinavian Journal of Work, Environment and Health*, *27*(5), 335–342. https://doi.org/10.5271/sjweh.622

Soderlund, L. L., Mckenna, E. A., Tastad, K., Paul, M., Lloyd, L., Mckenna, E. A., & Tastad, K. (2016). Prevalence of permanent threshold shifts in the United States Air Force hearing conservation program by career field, 2005 – 2011. *Journal of Occupational and Environmental Hygiene*, *13*(5), 383–392. https://doi.org/10.1080/15459624.2015.1123814

Suvorov, G., Denisov, E., Antipin, V., Kharitonov, V., Starck, J., Pyykkö, I., & Toppila, E. (2001). Effects of peak levels and number of impulses to hearing among forge hammering workers. *Applied Occupational and Environmental Hygiene*, *16*(8), 816–822. https://doi.org/10.1080/10473220119058

USAF. (2016). *Occupational Noise and Hearing Conservation Program* (Air Force Instruction 48-127). https://static.e-publishing.af.mil/production/1/af_sg/publication/afi48-127/afi48-127.pdf

Vyskocil, A., Truchon, G., Leroux, T., Lemay, F., Gendron, M., Gagnon, F., Viau, C. (2012). A weight of evidence approach for the assessment of the ototoxic potential of industrial chemicals. *Toxicology and Industrial Health*, *28*(9), 796–819. https://doi.org/10.1177/0748233711425067

Wathier, L., Venet, T., Bonfanti, E., Nunge, H., Cosnier, F., Parietti-Winkler, C., Campo, P., Pouyatos, B. (2019). Measuring the middle-ear reflex: A quantitative method to assess effects of industrial solvents on central auditory pathways. *Neurotoxicology, 74,* 58-66. https://doi.org/10.1016/j.neuro.2019.05.007