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An Evidence-base and Implementation Framework for Promoting Best Practices in Pharmaceutical Interventions for Hearing Loss (PIHL) Research

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An Evidence-base and Implementation Framework for Promoting Best Practices in Pharmaceutical Interventions for Hearing Loss (PIHL) Research

by

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Dissertation
Presented to the Faculty of the Graduate School of The University of Texas at Austin
in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

The University of Texas at Austin
May 2017
Dedication

The only way I survived balancing this program, this project, and work was with the constant support of my husband, Curtis, and son, Braxton, who ensured I was bathing with soap, eating real food, wearing clean clothes, getting sleep when time allowed, laughing and hugging every day. Thank you both for everything. I hope this work makes you both proud. I love you the biggest much.
Acknowledgements

This project was conceived and developed while serving in my role at the Department of Defense Hearing Center of Excellence (HCE). I would like to thank Col (retired) Mark Packer for his unwavering support of the development of the PIHL group and all of the initiatives borne thereof. Without his passion for research, vision for innovative translational platforms, and personal support for my professional and personal growth, this project would never have been. The entire HCE family have offered their unwavering support, encouragement, and specialized expertise (Dr. Lynn Henselman, Elsa Granato, Dr. Julieta Scalo, and Dr. Drew Fallon in particular), for which I am so grateful.

The PIHL group itself has offered so much to this project and its direction, lending world-renowned expertise at the other end of every call and email request. I am grateful to all PIHL group members: your enthusiasm for interaction and collaboration is inspiring and exciting to be a part of.

Some of my committee members were already part of the PIHL group when this project started – Dr. Colleen Le Prell, Dr. Carlos Esquivel, and Mr. Martin Slade – and some were not – Dr. Champlin, Dr. Rascati, Dr. Wilson, and Dr. Betancourt. To all of my committee members, I would like to thank you for your time, direction and obvious interest in this project, whether part of your daily lives already or entirely new to your scope of awareness, I recognize how fortunate I was to find each of you. Your unique and valued contributions are, I hope, evident in the work below.

Finally, this work is, by nature and intent, collaborative. As such, there are many hands that have touched the work herein, including, most obviously, my coauthors on manuscripts and presentations. Thank you for the learning experiences and your friendship.
ABSTRACT

Pharmaceutical interventions for hearing loss (PIHL) have many biological and physiological targets, highly variable study designs, incomparable outcomes, and no Federal Drug Administration (FDA)-approved drug after more than three decades of research. This project seeks to create the platforms and tools for scientific progress in this field with a novel model of translational research management. This effort includes a systematic review of PIHL studies to understand the key elements of study methods being employed across this field. A stakeholders group was developed to identify research barriers, determine prioritized issues to address, and provide expertise and consensus for the development of evidence-based Best Research Practices (BRPs).

Using PIHL literature obtained through standardized systematic review search methods, this effort identified, characterized, evaluated and correlated the methodological variables across the full translational scope of PIHL studies, from animal to human species. Publications from original reports of pre-clinical animal or human studies of interventions
to prevent or treat hearing loss or peripheral tinnitus caused by noise or blast exposure were included.

A total of 3,492 articles published prior to January 2017 were returned in the librarian-assisted, Boolean search. The final set of included articles were limited to noise- or blast-induced hearing loss targets only and data extraction was completed on 213 articles. The establishment of the PIHL network, comprised of over 200 interdisciplinary experts, provides the platform for discussion, consensus and development of state-of-the-science determinations and BRPs. Outcomes will be translated into recommendations for the consideration of the FDA, funding agencies, and primary peer-reviewed journal editorial boards as part of an overall knowledge dissemination, implementation and adoption strategy. Dissemination pathways, including journal special issues, conference presentations, as well as network discussion, consensus, and adoption are explored as key elements of the overall effort.

Early disseminations include 6 PIHL Newsletters, approximately 50 articles published or pending publication in four targeted peer-reviewed journals, and 9 presentations at national conferences.

Critical review and understanding of the state of current study methods provide the evidence-base to set norms and standards, which can avoid research waste, thus protecting study subjects and resources and more quickly benefit target patient populations.
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Chapter 1: Background and Literature Review

This chapter introduces hearing loss and the complex biology, physiology and metabolic pathways common to the special subsets of noise-induced and ototoxic-induced hearing loss (NIHL and OIHL, respectively). It also provides an overview of the current state of the science in these pharmaceutical technology development lanes, paying particular attention to explain their frequent overlap. The overview details barriers to scientific progress which have long plagued this stymied field of research, as well as the consequences of consistently heterogeneous methodologies.

Finally, the development of the Pharmaceutical Interventions for Hearing Loss (PIHL) working group is chronicled, with details of the group’s charter, objectives and accomplishments to date provided. This will reveal the rational for this study as well as the foundation for its translation activities and viable platform for future work.
1.1 **Hearing Loss**

The World Health Organization (WHO) released estimates of 700 million to 1 billion among the total population have a hearing loss, and that 360 million of those have a severe or disabling hearing loss (World Health Organization, 2015). Rates of hearing loss exponentially increase as we age (Lin, 2015). Some of the determinants of fate are in our genes, but a major contributing factor to hearing loss over the years is cumulative exposure to hazardous noise (Mills, 1973; Johnson, Nixon, & Stephenson, 1676; Tak, Davis, & Calvert, 2009; Lin, 2015; Smith, Beamer, Hall, Helfer, & Kluchinsky, 2015; National Institutes of Health, 2015). The inner ear houses a sensitive organ system that can be irreversibly damaged over time by intense noises and blast exposures, as well as blunt force trauma (Hirsch, 1966; Konradsson, 1999; Shah, Ayala, Capra, Fox, & Hoffer, 2014; Board on the Health of Select Populations, 2014; Littlefield, Pinto, Burrows, & Brungart, 2015). Unfortunately for these delicate body parts, it is an increasingly noisy world in which we are exposed to sounds on a daily basis, from lawnmowers to earbuds, which pose a threat to our ability to hear (Flamme, et al., 2012; Gilliver, Beach, & Williams, 2013). Moreover, noise exposure hazards are measured on an exponential scale, where it may take 8 continuous hours of 85 decibel (dB) exposure (such as the inside of a loud vehicle may produce) to sustain permanent hearing damage, yet there is risk of hearing damage from just 4 hours of exposure to 95 dB lawnmowers, and instant damage can occur by standing next to a firecracker that exudes 150 dB or more (Department of Defense Hearing Center of Excellence, 2016).
Men are more likely than women to report having hearing loss (NIDCD, 2015). Interestingly, in a study by Zelaya and colleagues in 2014, 45.3% of women stated that getting older was the main cause of their hearing loss, compared with 24.5% of men (Zelaya, Lucas, & Hoffman, 2015). Nearly 36% of men stated that long-term noise exposure was the main cause of their hearing loss, compared with nearly 11% of women. That difference may not be a difference of opinion but instead rooted in the facts about exposure and injury, currently listed on the National Institute for Occupational Safety and Health (NIOSH) statistics website page (NIOSH, 2014). Of all work-related illnesses, occupational hearing loss is one of the most common (14%), with approximately 22 million U.S. workers exposed to hazardous noise and another 9 million exposed to ototoxic chemicals annually. As a result, 10 million Americans have a noise-related hearing loss, with approximately 23,000 new cases per year and an estimated 82% of these cases come from the manufacturing sector (NIOSH, 2014). Among the most aurally at-risk workers are firefighters, musicians, miners, construction and manufacturing workers (NIOSH, 2014). These fields consistently populate national statistics for occupationally-related hearing injuries such as those collected by the Bureau of Labor Statistics, but militaries worldwide have likely contributed the largest number of hearing injuries since the first battles in recorded history.

First conceptualized by the US military, hearing conservation efforts have since been driven by programs and policies implemented by NIOSH and the Occupational Safety & Health Administration (OSHA) Occupational Noise Exposures targeting noise exposure
injuries, including surveillance, overall noise reduction and personal hearing protection strategies (Nixon, 1998). Despite these increasingly pervasive and comprehensive programs in the US, however, military hearing injury rates continue to climb exponentially, resulting in the number one (tinnitus, or “ringing” in the ears) and number two (hearing loss) most prevalent service-connected disabilities among Veteran’s for decades (Packer, 2013). According to the 2014 Veteran’s Benefits Annual Report, 2.4 million Veterans received compensation for auditory body system conditions, an 11% increase from 2013, which also saw a 14% increase from 2012 (Veterans Benefits Administration, 2012; Veterans Benefits Administration, 2013; Veterans Benefits Administration, 2014).

Identifying, describing, and addressing the factors responsible for this persistent occupational health risk within the military are complex tasks. Hazardous noise is pervasive in training and operational settings, and the military continues to make noisy weapons systems (guns and bombs) and vehicle platforms (tanks, trucks, ships and planes) because power and speed often equate to increased noise. Thus, there is a failure to implement noise controls because they come at the cost of mission advantage. The second preventative effort when noise reduction efforts fail is to block the noise from reaching the ear via hearing protection devices, yet these too have technological limitations; namely, ear insert devices (foam or flanged plug) and over-the-ear muffs cannot attenuate enough noise to protect from intense exposures. However, hearing protection devices are often not worn at all, or if they are, not worn properly to maximize noise attenuation (Bjorn VS, 2006; Widen SE, 2009). U.S. military Service members have reported that they do not wear
HPDs because they are uncomfortable, they forgot them, they do not believe they will help, or they degrade situational awareness on the battlefield. The phrase repeated often in survey and anecdotal Service member inquiries is, “I’d rather be deaf than dead.” Without alternative preventative measure, hearing loss is often considered “a cost of doing business” for a dedicated military career.

In addition to noise hazards, many ototoxic exposures pose a threat to hearing. Many prominent cancer fighting therapies as well as radiation treatments have well-documented ototoxic outcomes (Reddel, et al., 1982; Vietor, 2015; Choi, et al., 2013; Shi, An, Wang, Gao, & Y, 2014; Kuduban, Kucur, Sener, Suleyman, & Akcay, 2013; Shin, et al., 2014; Polony, et al., 2014). Chemicals and solvents including jet fuel found in both military and industrial settings have also shown ototoxic effects (Kaufman, LeMasters, Olsen, & Succop, 2005; Kim, et al., 2005). The fact that most people are exposed to some level of noise exposure, coupled with the damage that can occur with added ototoxic exposures has also been explored and shown to have synergistic effects in combination (Morata, 2007; Steyger, 2009).

1.1.1 NIHL and Ototoxic-Induced HL: The Theory of Metabolic and Oxidative Stress Pathways in the Inner Ear

The mechanisms of action behind noise-induced hearing loss are widely accepted to be two-fold: 1) mechanical damage to the cochlea caused by the physical vibratory trauma, which can lead to loss of blood flow and structural damage to hair cells and other cochlear supporting cells, and 2) the metabolic stress triggers which activate a cell death,
or apoptotic, pathway initiated by the formation of reactive oxygen species (ROS), driven by additional consequences of metabolic trauma such as vasoconstriction, leading to the loss of both hair cells and other vital supporting cells within the cochlea (Le Prell, 2007; Oishi & Schacht, 2011). These two mechanisms of action are not mutually exclusive nor mutually inclusive. While there are several potential points of intervention along both pathways, most opportunity lays in the latter, where the cascading effect of free radical damage can be prevented, mitigated or deterred at multiple lifecycle stages including:

- Mimicking the endogenous antioxidant defense of glutathione (GSH) to scavenge or prevent the formation of ROS via exogenous antioxidant therapeutic strategies.

- Increasing cochlear blood flow to maintain metabolic homeostasis thus severing the cycle of ROS production (Ohinata, Miller, Altschuler, & Schacht, 2000) (noise trauma causes vasoconstriction, leading to ROS production, which in turn causes vasoconstriction, causing further ROS production, *ad infinitum* or until cell death is achieved) via vasodilators, including steroids.

- Regulation of intracellular calcium homeostasis (modulation of calcium channels and calcium mobilization) to protect cells via
  
  - neurotrophic growth factors (NTF)
  
  - glucocorticoid mechanisms
  
  - protection from neuronal cell osmotic imbalance, swelling and rupture due to the calcium channel-excitatory amino acid glutamate
  
  - reduction of calpain- and calcineurin-mediated mechanisms of cell death
- Bcl-2 anti-apoptotic protein inhibitors of upstream calineurin
- Caspase inhibitors (receptor- or mitochondrial-mediated), including the JNK pathway and mitochondrial-mediated caspase prevention
  - Stress-activated kinases
    - Mitochondrial protection via NTF (El Idrissi & Trenkner, 1999) or
    - Auditory neural protection beyond the hair cells via NTF (Gillespie, Clark, & Marzella, 2004)
  - Synergistic activity among factors.

This process of oxidative stress and hair cell apoptosis is thought to occur over the course of anywhere from hours to several weeks. Threshold shifts that recover to baseline levels following exposure are termed temporary threshold shifts (TTS). Threshold shifts of up to ~50 dB immediately after a single noise exposure may recover completely, while more extensive immediate hearing losses are likely to result in permanent losses of hearing sensitivity (e.g. Bone & Ryan, 1978; Clark & Bohne, 1999). Continuous or repeated exposures to noise that only induce a TTS may also evolve to a permanent threshold shift (PTS) if repeated (Lonsbury-Martin, Martin, & Bohne, 1987), as occurs in occupational noise exposure. Therefore, PTS can be defined as noise-induced threshold shift that persists after a period of recovery subsequent to the exposure. In animal models, recovery has been reported for periods extending up to 3 weeks, therefore it may be premature to define a threshold shift as temporary until at least 3 weeks post-exposure, when a permanent threshold shift arises. However, the window of opportunity to intervene and
disrupt this pathway at a level of clinical relevance has repeatedly been shown to expire at roughly 72 hours post noise exposure (Kirchner, et al., 2012).

This same metabolic pathway can be initiated by both noise and ototoxic insults, thus many current viable PIHLs are also under investigation for those indications. Mechanisms of action of tinnitus are still largely unknown, yet investigations are also underway that also attempt to intervene along this same metabolic pathway for hypothesized peripheral tinnitus.

1.2 PIHL STATE OF THE SCIENCE OVERVIEW

Research to develop pharmacologic otoprotective agents to prevent, reduce, or reverse recent onset noise- or drug-induced hearing loss has been ongoing for several decades. First generation otoprotectants have typically been used clinically for other indications, occur naturally in foods, or are quickly broken down into other molecules used in cellular metabolism (Campbell, et al., 2007; Coleman, Littlesunday, Jackson, & Meyer, 2007; Le Prell, Gagnon, Bennett, & Ohlemiller, 2011; Kopke, et al., 2015). As such, they are natural targets for animal studies with an eye to translation to clinical trials. A number of agents fall into this category including antioxidants and micronutrients such as D-methionine, Vitamins A, C, and E and minerals such as magnesium. Second generation agents such as ebselen, AM-111 and SRC inhibitors have been shown to provide significant biologic protection given at lower doses (Bielefeld, et al., 2005; Harris, Hu, Hanauer, & Henderson, 2005; Coleman, Littlesunday, Jackson, & Meyer, 2007). There are other agents currently under study that are representative of this next generation of drugs. Some
can be administered orally but others may not be suitable for oral administration (Suckfuell, et al., 2014).

Across both generations, most formulations are currently pre-Investigational New Drug (IND) stage. Some do not fall under Food and Drug Administration (FDA) oversight because they are nutraceuticals and do not claim to prevent or treat a specific disorder (Kopke, et al., 2015). Several agents have acquired an IND, however, and because the Department of Defense (DoD) will neither approve human subjects research nor pharmaceutical distribution of any compounds without an IND/NDA, the developers of all technologies are forced into the IND process if they aim to test within DoD populations or market toward DoD pharmacy acquisitions (Department of Defense, 2008). No agent has acquired an FDA, nor any other national regulatory approval, for the prevention or treatment of hearing loss and the first such approval is likely several years away.

1.2.1 Barriers to PIHL Research

The reasons for over three decades of delay in PIHL development, compared to the FDA norm of 15-20 years, can be explained in large part by the difficulty for investigators in selecting appropriate study models and design. Currently, efficacy and effectiveness of interventions are disputable due to heavy variation in methods employed across studies, as well as the questionable quality of studies and reporting, and this disputable evidence delays entry into the FDA pipeline and stymies interest from potential study sponsors and commercialization partners.
Despite a plethora of promising animal study outcomes reported in the literature, the relatively few human studies completed to date have been disappointing, demonstrating a clear translational disconnect (e.g., Coleman et al., 2007a vs. Kopke et al. 2015). Rather than assume the compounds are simply ineffective in humans, it is better to understand some of the reasons why a particular compound may have failed to meet efficacy endpoints. There are, in fact, so many differences between the rigor of a laboratory environment and the real world variability of the open field environments in which these exposures are experienced in human populations, compounded with constraints that variability imposes on measurement capability, that they must be carefully examined.

1.2.1.1 Clinical Trials

Figuring out the realistic scenarios for clinical trials is the first step in determining rational targets for animal model research, and therein lies the problem: clinical trials for hearing loss, and noise-induced hearing loss in particular, are inherently challenging. The first challenge is the identification of a subject population that consistently experiences a high enough rate of hearing injury such that a clinical trial could be reasonably statistically powered to find an effect size. The quandary, however, is that upon identification of such a population, those overseeing the safety of that group would then be responsible for increasing protections to reduce or, ideally, eliminate the injury rate. Noisy military environments provide the most obvious solution to this problem in that military operational missions often include inherent high-stakes risks, including exposures to hazardous levels of noise, and yet must proceed to meet mission requirements. In targeting military
populations for PIHL clinical trials, investigators would also be responsibly ensuring that
the risks of clinical research participation are carried out on subjects representative of the
populations who would benefit from the resulting treatments (see The Belmont Report)
(National Commission for the Protection of Human Subjects of Biome Beha Resea, &
Ryan, 1978). However, those operational populations and environments are the most
logistically difficult to gain access to: restricted access to bases and populations, military-
to-study staff cultural differences, common deployments and relocations, unpredictable
exposures, and additional government bureaucracy all create delays or outright barriers to
the conduct of research.

Regardless of these challenges, a handful of investigators have been successful
identifying and navigating their way through a clinical study in military populations in the
U.S. and abroad (Pilgramm et al., 1985; Attias et al., 1994; Psillas et al., 2008; Kapoor et
al., 2011; Le Prell et al., 2011; Lindblad et al., 2011; Kopke et al., 2015). Study designs
were either for rescue indications, carried out in a clinical setting where patients presented
with hearing injuries from noise, or in a field setting where attempts were made to mitigate
noise hazards with a prophylactic dosing schedule. In both cases, issues persist that result
in the failure to find an effect size anticipated by more robust animal results. The biggest
factor for the rescue studies is timing of presentation. Effect sizes lower than anticipated
are often accompanied by a noticeable trend in improved treatment effect in earlier
intervention patients. Conversely, the biggest problem for prophylactic studies is finding a
large enough noise insult to prevent (see Le Prell & Lobarinas, 2016).
Other important factors to consider in the lack of translation from animal to human models include various elements within the primary domains of PIHL research for NIHL: namely, the 1) species, 2) noise exposures, 3) measures, 4) and drug administration variables.

### 1.2.1.2 Species

Selection of species for acoustic studies, and PIHL studies in particular, has been a topic of some debate. Next to the most easily bred and handled mouse and rat models, guinea pigs are the most often used in PIHL studies targeting NIHL. The latter are often selected due to their better hearing in the lower frequencies and larger ear anatomy, making surgical approaches more easily accomplished, than in their smaller rodent counterparts (Lynch et al., 2016). The chinchilla arguably has the more appropriate hearing range to serve as a comparator for humans and has the closest audiogram relative humans, with similar noise vulnerability at 4 kHz (Hammernick, 2008; Lynch et al., 2016). However, pharmacokinetics and pharmacodynamics of many PIHL agents remain unknown in the chinchilla (Lynch et al., 2016). Additionally, the variability in the lower- and higher frequencies demonstrated by Heffner & Heffner (2007) raise reasonable concern over the variation that occurs in translation between animal models and between animal-to-human models.
1.2.1.3 Noise Exposures

Military noises, usually mixed, or kurtotic, in nature, are not comparable to the laboratory noises delivered to animal models. Even attempts to replicate impulse noise exposures in the lab are often delivered as consistent, repeated pairs of impulses (Attias et al., 2003; Zhou et al., 2009; Bielefeld et al. 2011a; Müller et al., 2016). This does not replicate military battlefield sounds that include yelling, vehicle noise, blasts, etc. Such a chaotic environment with multiple insults may activate inherent defenses against hearing damage known as middle ear reflexes wherein the middle ear muscles contract enough to offer up to 20 dB of hearing protection (Danielson et al., 1991).

The durations of noise exposures are also inconsistent in the broadband studies where comparisons are made between hours or days of exposure to an animal model at high-decibel sound pressure levels (dB SPL), while workers in the real world are exposed for months or years to lower levels, with spikes of high intensity exposures periodically, such as daily mechanics work (continuous engine noise) with periodic metal clanging (impulse exposures). Moreover, most humans get periods of acoustic rest while they sleep and yet animal studies do not provide intermittent rest either.

1.2.1.4 Measures

Both the measures used to claim success in animal models and the timing by which they are collected differ significantly from human trials. As discussed above (see 1.1.1), noise-induced intra-cochlear cellular damage is a result of process that takes time to unfold. When animal studies report positive results at the 24-hour mark, they are not reporting
reduction in PTS), but of TTS. Conversely, if a rescue study includes patients after seven or more days have passed from the point of injury, the design is destined for negatively skewed results.

The translation of auditory brainstem response (ABR) results in animals to pure tone audiometry also deserves exploration. ABR relies on synchronous response to short tone pips whereas pure tone behavioral audiometry present the human patient with longer tones. While the correlation of ABR thresholds to audiometric thresholds in humans to humans, the same correlation between species is less understood (Gorga et al., 1985; Stapells & Oates, 1997). More problematic, the longer presentation of pure tones may still be detectable with NIHL while the same auditory neuropathy may not be detected by the shorter tone pips, missing synchrony in ABR testing (Le Prell & Brungart, 2016); therefore, it is difficult to ascertain whether ABRs in animals are more or less sensitive to changes than pure tone changes are in humans (Le Prell et al., 2004). Beyond physiological differences, laboratory animals exhibit predominantly homogenous anatomical and genetic profiles, while humans vary greatly in these areas, offering a multitude of points for translation to deviate.

There are many efforts ongoing to improve precision in human measures, including speech-in-noise tests (Le Prell & Brungart, 2016; Brungart et al., 2017); boothless audiometry that could create “mobile laboratories” and thus increased access to in-field populations (Meinke et al., 2016); advanced otoacoustic emissions testing for possibly greater sensitivity (Reavis et al., 2011; Konrad-Martin et al., 2016), or a standardized
subjective tinnitus measure (Henry, 2016; Hall et al., 2016), all of which present great opportunities for future clinical trial specificity and comparability. Unfortunately, for now, they simply underline the fact that we have a long way to go before fully understand what we are measuring in humans, much less how those effects can best be modeled in the laboratory.

1.2.1.5 Drug Administration

Effective doses in animal models are not always translated into the most effective doses for humans. This is not as simple as a mg-per-kg mathematical error. In the case of the Kopke et al. study conducted in U.S. Marine Corps recruits, the effective dose of n-acetylcysteine (NAC) delivered was lower than in comparable laboratory studies. Pills consisting of 900mg three times a day (TID) were administered to the first 600 Marines in the study. In a 70kg human, this averages to 12.8mg/kg TID, or a total of 38.6 mg/kg/day. NAC has shown some efficacy in animal models at 50 and 100 mg/kg when administered intraperitoneally (Bielefeld et al., 2007), but at 12.5mg/kg showed no difference from placebo (Clifford et al., 2011). If we assume a 9% bioavailability when given orally just for comparison (Olsson, Johansson, Gabrielsson, & Bolme, 1988), the largest dose given to the Marines would be 28.6mg/kg given orally, or approximately 2.6mg/kg absorbed from the gut into plasma, certainly lower than the lowest dose used in the laboratory.

Most laboratory work has been done via intraperitoneal, intravenous or intratympanic injection (IP, IV, or IT, respectively) routes, which makes the drug available for direct absorption into the blood stream or cochlea. The oral route, administered by
intragastric lavage in the laboratory (IG), is never totally absorbed through the gut, and subsequently circulates through the liver, where metabolism further reduces plasma levels. Bielefeld et al. compared IP dosing to IG administration (2005). Good hearing repair followed after NAC at 325mg/kg IP. When 325mg/kg was administered IG at the same dose, hearing showed significantly less recovery towards baseline. Careful consideration of dosing, concentration, route and timing of administration are all warranted.

In contrast to human studies, laboratory experiments have shown substantial efficacy of a variety of agents in equally variable delivery schemes, in experiments using different animal models, with variable noise exposures and measures. These differences could be responsible for the differences seen between the positive outcomes shown in laboratory studies and clinical trials. However, since essentially every element of the PICOS framework (Participants, Interventions, Comparisons, Outcomes) for conducting meta-analysis are heterogeneous across PIHL studies, the current body of literature offers no opportunity for comparison between outcomes.

1.2.2 Systematic Reviews, Meta-analysis & Methodological Heterogeneity

1.2.2.1 Review of Reviews

In a pilot review of 300 PIHL studies published in peer-review journals, the literature clearly showed that PIHL research has been conducted using largely heterogeneous study design elements. Thus, an attempted application to the Cochrane Collaboration, a global network and trusted source for systematic reviews and review
practices (www.cochrane.org), to conduct a systematic review and meta-analysis of PIHL clinical trials was rejected.

An initial Cochrane search found no articles focused on assessing the study design methods employed across the hearing, or most any other, field. Even in the Cochrane Review Group “Methodology Reviews”, no focus is given to homogeneity of methods across studies. Instead, the Cochrane Methodology group focuses largely on the methodology of conducting the reviews themselves, focusing largely on the development of more effective systematic review and/or meta-analysis research strategies as well as more effective clinical research strategies (i.e., analytic plans, assessing bias, hand-searching vs database searching, reporting standards adherence, recruitment and retention strategies, increasing telephonic data collection response rates, etc.). The few exceptions found in the literature exist primarily within the field of psychiatry to determine subjective metric validation.

Previous reviews were searched with the same strategy developed for original studies (see Chapter 2.2.2/Appendix C.1 below) with the omission of animal and human clinical trials search filters and the addition of a review search filter. Of the 120 articles returned, only 39 were found to be PIHL-relevant after screening title and abstracts. None among these was found which reviewed a body of literature for homogeneous study design with the aim to determine whether or not investigators were producing outcomes which could be systematically comparable. The PIHL-related topic reviews were conducted for outcomes of current treatments, or were reviewing the state of the science, the
pathophysiology of hearing loss and/or targets for intervention. Most reviews offer ideal material for background of this effort, but do not include any attempts to describe the current methodology utilized within this field of inquiry. The list of Cochrane reviews returned are listed in Table 1, and all summaries include issues encountered with heterogeneous measures, poor reporting, and overall poor study design.

Table 1. Cochrane PIHL-related review search results

<table>
<thead>
<tr>
<th>Review ID</th>
<th>Topic</th>
<th>Focus</th>
<th>Relevant Outcomes or Observations</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phillips et al. (2010)</td>
<td>Tinnitus Retraining Therapy (TRT) for Tinnitus</td>
<td>Outcomes</td>
<td>Only 1 study matched inclusion criteria; study quality issues prevent conclusions</td>
<td>Further RCTs needed</td>
</tr>
<tr>
<td>Person et al. (2016a)</td>
<td>Zinc for Tinnitus</td>
<td>Outcomes</td>
<td>3 studies included; heterogeneous and unvalidated measure instruments used; poor quality of evidence</td>
<td>Further RCTs needed</td>
</tr>
<tr>
<td>Person et al. (2016b)</td>
<td>Ginkgo Biloba for Tinnitus</td>
<td>Outcomes</td>
<td>4 studies included; heterogeneous populations; limited evidence</td>
<td>Further RCTs needed</td>
</tr>
<tr>
<td>Hoekstra et al. (2011)</td>
<td>Anticonvulsants for Tinnitus</td>
<td>Outcomes</td>
<td>7 studies included; Significant risk of bias; low clinical significance; meta-analysis of any + effect (yes vs. no) was conducted</td>
<td>Not promising</td>
</tr>
<tr>
<td>Martinez et al. (2010)</td>
<td>Cognitive behavioural therapy for Tinnitus</td>
<td>Outcomes</td>
<td>8 studies included; no significant effect on tinnitus (positive effect on depression); heterogeneous instruments used</td>
<td>Further RCTs needed</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Outcomes</td>
<td>Comments</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Baldo et al. (2012)</td>
<td>Antidepressants for patients with Tinnitus</td>
<td>Outcomes</td>
<td>6 studies included; trial quality low; heterogenous agents, instruments/measures; low statistical significance</td>
<td></td>
</tr>
<tr>
<td>Meng et al. (2011)</td>
<td>Transcranial magnetic stimulation for Tinnitus</td>
<td>Outcomes</td>
<td>5 studies included; poor reliability of results; poor study design/reporting; lack of long-term outcomes</td>
<td></td>
</tr>
<tr>
<td>Hobson et al. (2012)</td>
<td>Sound Therapy for Tinnitus</td>
<td>Outcomes</td>
<td>6 studies included; limited data of low quality</td>
<td></td>
</tr>
<tr>
<td>Bennett et al. (2012)</td>
<td>Hyperbaric Oxygen for Sudden Hearing Loss and Tinnitus</td>
<td>Outcomes</td>
<td>7 studies included; no significant improvements in hearing or tinnitus; low powered studies; methodological shortcomings; poor reporting</td>
<td></td>
</tr>
<tr>
<td>Hoare et al. (2014)</td>
<td>Hearing Aids for Tinnitus in People with Hearing Loss</td>
<td>Outcomes</td>
<td>1 study included; quality of this evidence is moderate to low (no blinding, outcome measure heterogeneity)</td>
<td></td>
</tr>
<tr>
<td>Wei et al. (2013)</td>
<td>Steroids for Idiopathic Sudden Sensorineural Hearing Loss</td>
<td>Outcomes, Risk of bias</td>
<td>3 studies included; high risk of bias; poor study execution; low power</td>
<td></td>
</tr>
</tbody>
</table>
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awad et al. (2012)</td>
<td>Antivirals for Idiopathic Sudden Sensorineural Hearing Loss</td>
<td>4 studies included; low risk of bias; heterogeneous measures used; poor reporting of AEs; no meta-analysis possible</td>
<td>Further RCTs needed</td>
</tr>
<tr>
<td>van As et al. (2016)</td>
<td>Medical Interventions for the Prevention of Platinum-induced Hearing Loss in Children with Cancer</td>
<td>3 studies included; low quality of evidence: “pooling of results was not possible and all studies had serious methodological limitations”</td>
<td>Further RCTs needed</td>
</tr>
<tr>
<td>Agarwal et al. (2009)</td>
<td>Vasodilators and Vasoactive Substances for Idiopathic Sudden Sensorineural Hearing Loss</td>
<td>3 studies included; “there were differences in the type, dosage and duration of vasodilator used in each study. Due to the degree of heterogeneity the results could not be combined to reach a conclusion”</td>
<td>Further RCTs needed</td>
</tr>
<tr>
<td>Simpson et al. (2011)</td>
<td>Oral or Topical Nasal Steroids for Hearing Loss Associated with Otitis Media with Effusion in Children</td>
<td>12 studies included; med- to high quality; “No study documented hearing loss associated with OME prior to randomization”; limited follow-up; “there was significant heterogeneity between studies (P &lt; 0.01, I² = 69%).”</td>
<td>Further RCTs needed</td>
</tr>
</tbody>
</table>

Beyond the Cochrane reviews, very few PIHL-related reviews followed a truly systematic approach. Critical review and understanding of the state of current PIHL methodology utilization and trends are needed provide the evidence-base to set norms and standards for future investigators to design studies which produce comparable study
outcomes. Further, a critique of the literature for reporting in accordance with “Animal research: reporting in vivo experiments” (ARRIVE) (Kilkenny et al., 2010) or “Consolidated Standards of Reporting Trials” (CONSORT) (Schulz et al., 2010) international guidelines will expose shortcomings within this field and illuminate areas for improvement.

1.2.2.2 Making the heterogeneous homogenous

There are currently few norms or standards for study design elements employed in PIHL research studies. A 2012 standard for reporting hearing outcomes in all clinical trials with hearing measure domains included was the first such attempt to provide best practices in research, but did not apply solely to PIHL studies (Gurgel et al., 2012). Moreover, this standard, adopted by the American Academy of Otolaryngology – Head Neck Surgery (AAO-HNS), as well as that organization’s affiliated journal publication, *Otolaryngology–Head and Neck Surgery* (Sage) and *Otology and Neurotology* (Wolters Kluwer), was not widely accepted by the PIHL investigators community. In a letter to the editor, Dr. Deborah Carlson, then-president of the American Academy of Audiology, refuted the methods employed to reach the purported standards as well as the implications for PIHL studies themselves (Carlson, 2013). Specifically, she refuted the standard by stating the following:

“While we appreciate and concur with the concept of standardized reporting methods, we point out that any such standard requires investigation for validity and reliability prior to blanket implementation. Such testing must include the intended clinical trial populations, consider variability in the intended outcomes of various
clinical trials, and must be published in peer reviewed journals. The examples used in Gurgel et al. are hypothetical, thus they are untested and provide no guidance on the efficacy of statistical analyses of their proposed data sets.

“We also request that any suggested guidelines or standards be circulated through the American Academy of Audiology and the American Speech Language and Hearing Association for comment, review and acceptance by a vote of the board of directors as is standard practice.”

Failing to include key stakeholder groups in the formation or review of these recommendations ultimately led to non-adoption by excluded groups. More problematic, the failure to ensure recommendations were thoroughly evidence based weakened the validity, application, and claim of authority.

Other than Gurgel et al., the only other discovered PIHL-relevant effort focusing on creating research design standards comes out of the United Kingdom-based James Lind Alliance (JLA). The JLA “aims to raise awareness among those who fund health research about what matters to both patients and clinicians,” and in their Tinnitus Priority Setting Partnerships (PSP), the focus is entirely on tinnitus research (Hall et al., 2013). Based on outcomes from Hoare et al. (2011), the JLA took note that the heterogeneity of tinnitus etiology, pathophysiology and clinical characteristics all contribute to the wildly heterogeneous study designs employed and they are developing a comprehensive research strategy that takes patient and provider priorities and validated measure instruments into
consideration (Hall et al., 2013 & 2015). Of primary concern to the group currently is the creation of core and peripheral outcomes, accomplished through both a systematic review of tinnitus outcome domains and instruments, much like the effort undertaken herein, as well as the execution of a Delphi survey and systematic appraisal of instruments by a group of stakeholders (Hall et al., 2016). The similarities between this effort for tinnitus research and PIHL research is encouraging, particularly in light of the overlap between the domains and the interaction between the JLA’s PSP and the DoD Hearing Center of Excellence (HCE)’s PIHL working group.

1.3 THE PIHL WORKING GROUP

The HCE was enacted by Congress in Public Law 110-147, the Duncan Hunter National Defense Authorization Act for Fiscal Year 2009 “focused on the prevention, diagnosis, mitigation, treatment and rehabilitation of hearing loss and auditory system injury” with a focus on collaboration with the Department of Veterans Affairs (VA) (110th United States Congress, 2008). The HCE stood up in May 2010 with a mission “to optimize operational effectiveness, heighten medical readiness, and enhance quality of life through collaborative leadership and advocacy for hearing and balance health initiatives” through the efforts of five branches: Prevention, Clinical Care, Informatics, Research and Operations (Department of Defense Hearing Center of Excellence, 2016). By 2011, the PIHL Group was chartered to address the pressing need to expedite development and translational progression of this field (see Appendix A). This group was established to provide subject matter advice and coordination in the development of otoprotectant and/or
otorescue pharmaceutical agent research methodology, efficacy standards and implementation practices across the DoD and throughout the acquisition lifecycle, including all research and development (R&D) phases.

The PIHL WG establishes relationships connecting all stakeholders within the DoD, including the HCE, pharmacy, R&D funding agencies, advanced development operations, management, acquisitions, requirements generation, training, testing, sustainment, and public health agencies. This PIHL stakeholder consortium is then connected directly to leaders in the field throughout academia, biotechnology and big pharmaceutical companies as well as other U.S. federal stakeholders and gatekeepers like the National Institutes of Health (NIH) and FDA, and foreign institutions with synergistic interests. These relationships are entered and sustained under the common goal to advance the field forward as expediently and efficiently as possible through evidence-based and coordinated research practices.

1.3.1 PIHL Group, Mission, and Objectives

Both military and civilian noise threats continue to claim casualties. Degradation of quality of life and limitations in communication, opportunities and performance can be expected to continue to escalate, marginalizing significant portions of the nation as well as putting our nation’s military warfighters at a severe disadvantage. Advancements in the PIHL arena are critical to ebbing this tide. The HCE founded the PIHL for these purposes; to support the research and development of translational therapies for the prevention and
rescue of hearing loss so that our Service men and women don’t have to choose between
duty and deafness.

The specific goals outlined by the group are to:

• Review existing state of the science;
• Determine minimal acceptable level(s) of functional performance for any potential
  translational agents;
• Develop and validate evidence-based laboratory, animal and clinical assessment
  protocol methodology guidelines;
• Recommend appropriate standards and technologies; and
• Provide a platform for collaboration, discussion, networking and progress.

To accomplish these goals, the working group was established with an open-
invitation to all interested parties starting with investigators collaborating with or funded
by the DoD. Beginning with < 15 members at the first meeting, the group now stands at
176 members, representing 100 organizations (internal DoD agencies or programs, or
distinct agencies, institutions, companies, etc.) from 6 countries. The group consists of
leaders and subject matter experts from the DoD, Department of Veterans Affairs (VA),
NIH’s National Institute for Deafness and Communication Disorders (NIDCD), Centers
for Disease Control and Prevention (CDC) National Institute for Occupational Safety and
Health (NIOSH), as well as world-renowned experts in this field across academia, industry,
non-governmental organizations (NGOs) including non-profit foundations, and
international collaborators. Figure 1 displays the diversity of the group across participating
organizational origins.
Figure 1. PIHL Group Composition

The group is an assembly of leaders in their field, all busy with their own full-time jobs, and thus the call to contribute to the PIHL mission was strategically designed to maximize interest and participation. Establishing the PIHL group by a U.S. military organization provided a unifying superordinate goal of contributing selfless effort toward a patriotic mission. Beyond the patriotic mission, tangible benefits of participation – including open opportunities for publication, up-to-date and consolidated source of state-of-the-science and funding information, and direct lines of communication with gatekeeper agencies – added considerable draw to the all-volunteer group. Word-of-mouth helped spread interest in the group and early productivity (discussed further in the following sections) created a reputation of legitimacy. This newly shared identity successfully built relationships among groups traditionally intimidated by one another, competing against
each other, and/or known only by reference material bylines prior to the PIHL group initiative.

The expertise gathered together under the unified umbrella of the PIHL group provides several avenues for progress. First and foremost, it develops the knowledge core needed to create valid, trusted guidance. Second, it creates a collegial platform for communication among potential partners along the commercialization pathway, from bench-to-bedside researchers to sponsors and investors. These relationships are not always easy to forge, because many of the former, academicians and laboratory scientists, often do not have experience or resources at hand to gain direct access to the latter, the venture capitalists and big pharmaceutical representatives. It also adds the gatekeepers within regulatory agencies into discussions earlier than usual, providing opportunity to dialogue, understand expectations, and work through unknowns. As research funding pots continue to shrink, the direct connection to funding sponsors and immediate awareness of program announcements through watch lists developed and distributed by the HCE are also unique to the PIHL group. The HCE is able to provide strategic coordination of and advocacy for PIHL research across federal funding portfolios, providing the latter with the cross-organizational awareness and scientific updates. These agencies can turn to the PIHL group at large for targeted inquiries for information as well, maximizing their own investment strategies. Finally, the HCE, through the PIHL initiative, has taken on the task of understanding, targeting, and coordinating investigators with relevant patient populations for clinical trials within the DoD. This obligation includes determining the populations
most as risk for unpreventable hazardous noise exposures, coordination with the leadership of these populations to gain access and minimize disruptions to operational missions or research oversaturation.

Upon review of the mission and operational model of the United Kingdom’s “Action on Hearing Loss” Translational Research Initiative for Hearing (TRIH) (Figure 2 below, accessed from: https://www.actiononhearingloss.org.uk/your-hearing/biomedical-research/trih.aspx), it became apparent that the PIHL group shares a similar focus. Figures 2 and 3 below show both the TRIH and PIHL models side-by-side for comparison. While they both share domains of interest, there are notable differences which include the TRIH’s ability to actually fund research, while the HCE does not. Also, Action on Hearing Loss is a large non-profit entity comprised of over 2,000 staff and volunteers which solicits donations to operate. In comparison, the PIHL Group is led by one person at roughly 10% effort, with support provided by up to an additional eight HCE personnel at roughly 5% effort each. The PIHL group survives on the enthusiasm of volunteers across segments of its membership. The TRIH has been among those most enthusiastic and their willingness to collaborate and share models and reports has benefitted the progress of the PIHL group tremendously. The TRIH’s participation in PIHL activities has created a synergistic relationship, serving to extend the similar missions of both organizations across the Atlantic more thoroughly. The TRIH focus on funding supports international translational research in hearing loss and tinnitus; consultancy provides expert advice and guidance to industry and investors, including marketing opportunities; partnerships are facilitated
between industry, research groups, and therapy experts internationally; and patients are encouraged and empowered to get involved in research.
1.3.2 PIHL Operations

1.3.2.1 Symposium

In 2012, the HCE organized the first PIHL Symposium, co-sponsored by the Office of Naval Research (ONR)’s NIHL Program to discuss state-of-the-science, determine gaps, and develop roadmaps for progress (see Appendix B.1). The two-day agenda attracted 54 attendees. As a result of this meeting, 8 topic areas were defined as gap requirement targets, including 1) Sound/Noise Exposures, 2) Clinical Trial Guidelines, 3) Animal Models, 4) Statistical Packages, 5) Genomic Considerations, 6) Delivery Methods, 7) TTS vs. PTS and 8) DoD Requirements. These topic areas became the first committees of the PIHL group. However, after 12-18 months, enough time for monthly meetings to define objectives and set taskers, it was clear that the volunteer group members did not have the bandwidth to tackle all 8 domains concurrently (see Table 2). Thus, just prior to the 2014, it was decided to focus on the top 3 committees: clinical, animal, sound. The remaining topic committees determined that systematic review results were required to accomplish tasks they had outlined.

Table 2. PIHL Group Committees

<table>
<thead>
<tr>
<th>PIHL Group Committees (2012-2013):</th>
<th>Objective</th>
<th>Goal(s)</th>
</tr>
</thead>
</table>

30
<table>
<thead>
<tr>
<th>Table 2 (continued)</th>
</tr>
</thead>
</table>
| **Clinical Trial Testing Guidelines** | To contribute to the development, evaluation and dissemination of Clinical Trial Guidelines for research conducted in pharmaceutical interventions for hearing loss in collaboration with the relevant professional academies/societies | 1. Review state of the science  
2. Develop academy (AAO & AAA) relationships  
3. Determine which testing mechanisms are good candidates for standardization/guideline attempts |
| **Animal Models** | To provide formal guidance, best practices, and/or publications on standards for study design in preclinical/basic science studies | 1. Review state of the science  
2. Discuss and come to consensus on the issues re: homogeneity of animals and lab settings  
3. Determine whether basic science design can be more realistic/applicable to human models  
4. Work with "Sounds" committee to determine standards for animal models  
5. Non-human primate (NHP) models development  
6. Determine appropriate tests (histophathy, physiology, behavioral) |
| **Sound Exposures** | To provide formal guidance, best practices and resources for researchers conducting noise exposure experiments and research; Provide recommendations to ensure the safety of human and animal test subjects in noise exposure studies; Identify groups that are at-risk of being exposed to high levels of noise | 1. Develop guidelines for noise recordings  
2. Create a compendium of noise exposure systems  
3. Review state of the science  
4. Develop sound exposure guidelines to ensure safe research practices  
5. Identify High Risk Groups |
| DoD Functional Requirement | To make pharmaceuticals more useful in combat situations and develop a DoD functional requirements guidance document specifying shelf life requirements, dosing in theater, and storage temperature requirements | 1. Review state of the science  
2. Identify specific DoD constraints  
3. Work with Delivery Methods Committee to create "Best Delivery by DOD Constraint" matrix  
4. Determine price point per dose |
|---------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| TTS vs PTS                | To provide formal guidance, best practices, and/or publications on standards to define TTS and PTS; along with recommendations of primary and secondary measures of outcome to consider | 1. Review state of the science  
2. Create standards to define injury  
3. Monitor safety and use of TTS in research  
4. Define other outcome measures to consider |
| Delivery Methods          | To provide comprehensive understanding of various drug delivery methods, their state-of-the-science, and implications for performance and/or efficacy | 1. Review state of the science  
2. Work with DoD Functional Requirements Committee to create "Best Delivery by DoD Constraint" matrix |
| Statistics                | To create standardizations and/or guidance for statistical measures to be performed in studies regarding pharmaceutical interventions for hearing loss, which includes creation of a minimal statistical battery for various types of studies | 1. Review state of the science  
2. Obtain/determine definitions of terms to be used in statistical analysis  
3. Create list of the different possible types of studies  
4. Create standardizations/guidance  
5. Create minimal statistical battery |
| Genomics                  | To provide formal guidance, best practices, resources/collaborators/subject matter experts (SME)s and/or publications on standards to collect, analyze and/or report genomic elements of PIHL study | 1. Review state of the science  
2. Determine the kind of collections which can be standardized to feed into a global repository |
Table 2 (continued)

| Ototoxicity\(^1\) | To advance our understanding of the varied mechanisms of ototoxicity, and promote translation of potential medical interventions and otoprotectants into clinical practice | 1. Discuss ototoxicity research and clinical practices  
2. Develop and distribute publications for ototoxicity, prevention, and otoprotection research  
3. Develop and distribute best clinical practice guidelines relating to ototoxicity  
4. Create and maintain an "ototoxic drug effects" hearing system repository  
5. Facilitate development of pharmaceutical interventions most relevant to the Active Duty, Veteran, and Civilian populations. |

The 2014 meeting aim and focus was to provide a platform for discussion and dissemination of the advancements made by the group since 2012 and to refine directions forward (see Appendix B.2).

1.3.2.2 Teleconference

The PIHL group, dependent upon volunteered time, espouses a flexible structure and cadence. Quarterly teleconferences are held to disseminate accomplishments, discuss issues facing the working group and plan future lanes of effort. All are welcome to attend once a curriculum vitae, Conflict of Interest Disclosure, and Non-disclosure Agreement are

\(^1\) In 2016, the wave of interest was cresting toward ototoxicity. The flexibility afforded by the PIHL group model to wane and wax with the prevailing enthusiasm accommodated the formation of the first new committee since 2012, with similar goals and tasks as previous committees, aligned to the PIHL mission. This garnered many new members, renewed interest from long-time participants, and a broader scope of expertise into the group.
submitted to the HCE. The committees meet during between-months and are intended to tackle tasks and provide a forum for issues that are necessary to discuss and reach consensus on products. The larger group meetings share committee progress updates, as well as relevant news to the broader group such as funding announcements, pivotal publications, new member introductions, and strategic and logistic planning for the group (i.e., new directions, future meetings, etc.). Participation is typically 25% of membership across group/committee calls, with a mix of consistent participants and many who rotate as schedules allow, and more still who await meeting minutes and outcomes to track and reply electronically.

1.3.2.3 Other Communication

Primary disseminations to the public are made through the HCE website (http://hearing.health.mil/) where PIHL information and Newsletters (see Chapter 4.1.2) are posted.

1.4 Looking Forward: Policy and Research Culture

1.4.1 Evidence-Based Practice (EBP) to Best Research Practices (BRPs)

Evidence-based practice (EBP) in clinical medicine was developed in the 1970s, “integrating individual clinical expertise with the best available external clinical evidence from systematic research” (Sackett et al., 2000). This approach retains the expertise gained over a professional career of treating patients of the individual provider and also demands
incorporation and awareness of the best evidence, including novel advancements. Implementing best practices can avoid wasteful tests and treatments by maximizing efficiencies, and thus EBPs also contribute to cost-effective healthcare delivery (Thorne, 2003). Yet the same concept has not been widely applied to research practices: of the best research practices, or “BRPs”, there are very few and they are poorly disseminated or adopted. A good example of this can be found with the reporting guidelines, CONSORT and ARRIVE, posed for reporting results of clinical trials and animal research, respectively (Schulz et al., 2010; Kilkenny et al., 2010), and internationally adopted as standardized best practice. Yet their recommendations remain widely unknown to investigators and thus are still rarely incorporated into the peer-review process for publication. As a result of this void in guidance (or at least in well-disseminated guidance), research in general – and PIHL research in particular – has no roadmap for developing BRPs nor many examples of organically developed BRPs. Ergo, research design commonly develops at the discretion of the investigator (and possibly the project’s funding sponsor).

In a recent book dedicated to “Translational Research in Audiology, Neurotology and the Hearing Sciences,” authors Le Prell & Lobarias (2016) close out their discussion with the challenge to develop standardized metrics across PIHL studies in order to reach comparable results. And as early as 2003, it was recommended that the audiology community increase their ability and habit of performing quality assessment of articles:

“[Audiologists] need to be able to assess and analyse research findings and to question the validity of studies that promote new treatments and technologies. They
need also to question the validity of research findings and, as a professional group, to promote research into better diagnostics and clinical practice. Without a critical eye the audiologist is vulnerable to poor quality research and unsubstantiated or inflated claims about treatments or from companies eager to sell their products in a competitive market” (Thorne, 2003).

Considering the plethora of nutraceutical agents on the market today with claims, unsubstantiated by an FDA approval, to “restore your natural hearing without prescriptions or hearing aids” (http://hearinglosspill.com/), it is more important than ever that the professional providers for hearing degraded patients or serving the populations at risk to hazardous noise exposures are well informed about the state of the science. And how can they interpret results as variable as PIHL research is hypothesized herein to be? If the knowledgeable SMEs on the PIHL committees cannot compare outcomes, how can the average audiologist or otologist be expected to?

Like hearing loss, tinnitus has many theorized etiologies, from emotional to central to peripheral, creating many targets for intervention and equal, if not more, numbers of measures to evaluate efficacy across these domains. The broad assortment of trial designs and uses of outcome measures prevents meaningful comparisons, including meta-analysis, for tinnitus research just as it does in hearing loss research (Hoare et al., 2011). Recognizing this critical gap in the heavily variable field of tinnitus and building on the recommendations of the attempted systematic reviews for tinnitus outcomes discussed above (section 1.2.2.1), Hall et al. designed a systematic review of outcome domains and
instruments used in the published clinical trials of adult tinnitus treatment (2016). This review focused solely on outcome measures for the purpose of driving research design toward comparability and provides an excellent roadmap for hearing loss research to follow. The contributions of these efforts toward BRPs is exciting to see and is a positive confirmation of the PIHL group consensus for the need to fill similar gaps across the hearing loss specialties.

Beyond comparability, focus on reproducibility, sound statistical design, and negative reporting bias are all growing concerns in science overall (Ioannidis, 2017). High reporting quality is required to improve reproducibility and raw data are encouraged to be made available for statistical reproduction. Given the complexity of auditory research variables, PIHL research is ripe for scrutiny of statistical analysis plans utilized and possible reform, starting with the definition of hearing loss itself across measures used (Slade, 2015).

The development of evidence-based medicine, and the resulting EBP’s, driven by the need to ensure both clinical and cost-effectiveness in health delivery equates to the need to ensure scientifically sound and cost-efficient conduct of research. To this end, the development of BRPs holds great promise. Provided with the roadmaps proven to produce the least waste and most comparable, reproducible outcomes, investigations could be optimized for successful translation.
1.4.2. Journals and Funding Sponsors: Carrots and Sticks

Both sponsors and disseminators of research – the funding sponsors and publishers – have played pivotal roles in the adoption of change within the scientific community. When ethical standards strengthened, so too did the standards of respected journals for publication. It is difficult to find a paper published these days with human subjects which does not address the Institutional Review Board (IRB) approval and informed consents acquired prior to conducting human studies or the humane treatment of animals used in institutionally approved and accredited laboratory studies. Most journals have entire online sections and toolboxes devoted to ethics in research. There is even a coalition of premier journal editors and publishers known as COPE – the Committee on Publication Ethics – devoted to promoting integrity in research and its publication (publicationethics.org). These resources exist because a problem existed and continues to exist which demands attention and mitigation, and they exist because publication is a primary source to affect change in those behaviors. Journals control publication decisions, and thus, to some extent, they control the fate of investigators’ dissemination pathway, their career notoriety, and future funding review scores. When journal editors and publishers take up dedicated efforts to address the issues of scientific integrity posed by poor study design and substandard analytic methods, then here, too, change can be enacted with the simple use of publication incentives. The AAO-HNS and its affiliated publication, Otolaryngology -- Head and Neck Surgery, took this step, as medical professional societies are perhaps more accustomed to terms of EBP guidance, in publishing the reporting standards posed by Gurgel et al. through
an Academy committee effort (Gurgel et al., 2012). While these efforts did not result in the perfect outcome with welcome adoption (Carlson, 2013), it does set the stage for a publication to make known its plans to only accept for publication articles which adhere to a new set of minimum requirements, and that has intent alone has value.

While publication is more of a lagging motivator in that the publication pathway is sought after a project is finished, the leading motivator for research design standardization must come from the funding sponsors and regulatory approval gatekeepers of research activity. There is obviously no better time to affect changes to a poorly designed study than before it begins. And while publication rejections are surely a “carrot” to do things differently next time around, there is no sharper “stick” than withholding funding or delaying an IRB or IACUC approval.

1.4.3. The FDA: Evolving the Clinical Trial Requirements

PIHL research is in an unfortunate position when it comes to translating into clinical trials in that neither a prophylactic nor a rescue trial design is easily executed. For the former, investigators must find a population cohort which is 1) exposed to an hazardous noise from which they cannot possibly be protected (to abide by ethical research practices); 2) homogeneous enough to eliminate as many confounding variables and exposures as possible; 3) accessible for a time span required to capture injury exposure and protective effect. For the latter, investigators must find patients who present with acoustic trauma within the brief metabolic pathway timeframe of a few days (Campbell, Hammill, Hoffer, Kil, & Le Prell, 2016). In addition to the ethical and logistical challenges discussed, there
are inconsistencies within the regulatory bodies that govern both pharmaceutical approvals to market and the most obvious research populations: the FDA and DoD, respectively.

The FDA sits under the Department of Health and Human Services (DHHS) and is responsible for one of the most highly regulated industries in the United States, the pharmaceutical industry (Carpenter, 2004). However, a careful examination of the FDA’s history can easily demonstrate the agency’s policy process has been quite receptive to its stakeholders and adaptive to change over the decades (see Chapter 5.3.2 for more detail). Such an understanding of the workings of the FDA can in turn show the way for development in lanes that do not fit neatly into the current paradigms offered by the agency. The hearing loss research interest groups stand at a pivotal juncture where the possibility of a successful development pathway is only an organized response to the FDA away.

Beyond the policy changes at the Federal level, however, real change will require unified action across stakeholder groups – to include funding agencies, top-tier scientific journals, and professional societies – all to encourage and enforce recommended “best research practices”. If funding agencies are the carrot to require appropriate study design prior to funding award, publishers have historically been the stick, exercising their right to deny publication to any papers which do not display adherence to best practices [see SAGE Publishing’s “Ethics & Responsibility” for an example of rigid standards expected (SAGE Publishing, 2016)]. Furthermore, journals also set the standard by which peers judge one another. Nonetheless, scientific community reactions to imposed requirements can be adverse, creating a challenge for consensus. Gurgel et al. (2012) published an article in
Otolaryngology – Head and Neck Surgery (the publication for the AAO-HNS) recommending new reporting standards for hearing outcomes in clinical trials. The otolaryngology community who wrote the article did not include audiology stakeholders in the creation of the document yet it was adopted by three major otolaryngology journals – Otolaryngology—Head Neck Surgery, Otology & Neurotology, and Laryngoscope. Controversy ensued over the generalizability and applicability of all requirements, prompted by prominent members of the audiology community publishing a letter to the editor. And when journals are not setting outright standards, they can still weigh in on topics they publish with added editorial notes attached to papers, as in the case of Le Prell et al.’s paper concerning a potential ethical design concern with noise exposure to healthy subjects (Le Prell et al., 2012). Where consensus is questionable or actual risks are debatable or best practices simply are not yet empirically known, journal editors and editorial boards can play pivotal roles in knowledge management simply through the power of publication and the implied endorsement of that disseminated knowledge.

1.5 SUMMARY

Hearing is a critical sense. One of the most pervasive injuries in both industrial and military settings, hearing loss negatively affects performance (Brungart, 2014; Peters LJ, 1990) and is also linked to a degraded overall quality of life and multiple co-morbidities, including dementia and other cognitive declines (Lin, 2015). Through the PIHL group, the need has been clearly identified for alternative protective strategies, such as pharmaceutical agents, to interrupt the biological pathways that cause permanent hearing injury and
subsequent irreversible hearing loss. Through an experiment in translational science administration, this project concurrently 1) conducted a comprehensive systematic review of the state of the science of pharmaceutical interventions for hearing loss; 2) developed a working group of interdisciplinary, interagency, international subject matter experts and stakeholders; 3) advocated for a DoD acquisition plan for clinical/advanced development of PIHL technologies; 4) developed relationships with professional society leadership; 5) and published a series of special editions/issues in major field-related journals to both establish relationships and credibility with editors and editorial boards. These efforts are intended to organize and create translational efficiencies across one specific field of science, bringing technologies to patients faster with a stronger evidence-base.
Chapter 2: Methodology

This chapter documents the methodology developed and followed to execute the systematic review of peer-reviewed literature on the topic of pharmaceutical interventions for noise-induced hearing loss. Additionally, the methods used for translation of the resulting evidence base is detailed herein. These two subsections make up Primary Aim 1 and Primary Aim 2, respectively, and each aim will be defined in this chapter, accompanied by their detailed approaches and limitations.
2.1 **SPECIFIC AIMS**

This study entailed a novel type of descriptive review of peer-reviewed PIHL studies to understand the various elements of study methodologies being employed across this field. Analyses were conducted to identify any correlations among study methodology variables and injury outcomes. This assessment did not focus on the safety or efficacy outcomes of the compounds being studied but instead on the research designs in PIHL investigations, with the objective of producing sets of “best research practices” (BRPs).

Using PIHL literature obtained through systematic review methods consistent with current standards, the effort identifies, characterizes, evaluates and correlates the methodological variables across PIHL studies, from animal to human. In so doing, the hope is to contribute to the current understanding of the state of the science and identify any trends across studies in this field which can begin to pave the way toward standardization in PIHL study design.

2.1.1 **Primary Aim 1**

This study seeks to define, identify, characterize, and evaluate primary study method variables across PIHL literature including: study design, in vivo model selection, hearing injury exposures, hearing measures, drug pathway, drug mechanism or class, drug delivery, as well as study and investigator demographics.
2.1.1.1 Secondary Aim 1

Using relevant standards and guidelines for reporting as benchmarks, assess and describe the quality of reported studies.

2.1.1.2 Secondary Aim 2

Identify, evaluate and summarize any trends of correlation between methodologies utilized in study designs which could contribute to a “criterion standard” for future study design guidance.

2.1.2 Primary Aim 2

This project aims to establish the framework through which the findings from Aim 1 may be translated into best research practices guidance and policy recommendations designed to inform the FDA, federal funding agencies and relevant journal editorial board audiences as gatekeepers and influential stakeholders to the primary adopters being targeted: namely, the investigators of PIHL research.

2.2 Research Strategy/Approach/Methodology: Primary Aim 1

This systematic review was registered with PROSPERO (registration number CRD42015027009) on October 11, 2015.

2.2.1 Eligibility Criteria

This study aims to critique the full spectrum of PIHL research from its inception. Therefore, a comprehensive search strategy was used without date limitations, with the
exception of limiting included studies to English language or English translations, which
will be noted as a limitation in all resulting disseminations. PICOS (Patient, Intervention,
Comparison, Outcome, Setting) domains were intentionally established very loosely in a
published protocol (see PROSPERO listing above). Publications that reported findings
from original reports of pre-clinical animal or human controlled trials of chemical
interventions to prevent or treat hearing loss or peripheral tinnitus caused by noise or blast
exposure in any setting were included. Peer-reviewed journal status was tracked but not an
inclusion/exclusion criteria. Conference proceedings, editorials, non-original research (i.e.,
reviews or duplicative publications of the same study) and retrospective or case studies
were excluded. Due to the many studies which include hearing injuries as secondary
outcomes or adverse events, hearing loss (or related search term) as a primary indication
for intervention was mandatory for inclusion. This eliminated many oncology intervention
studies where hearing loss measures were included to track side effects, for example.
Studies designed to test hearing regeneration were also excluded as a lane of research
targeting entirely different biological processes. Interventions for ototoxicity, Meniere’s
disease, congenital deafness, sudden sensorineural hearing loss, age-related hearing loss or
other diseases of the ear (i.e., otitis media, otosclerosis, etc.) were also excluded. Further,
studies using a non-chemical intervention, including acupuncture or devices such as
hearing aids or middle- or inner-ear implants, were excluded.
2.2.2 Search Sources and Key Concepts

The search was conducted by a mixture of quasi-manual and automatic searches. The quasi-manual search includes 10 years of work in this field, including starting and maintaining the PIHL Working Group described above, which has resulted in the capture of relevant reports written by or for the DoD by contractors or employees, as well as several study reports written outside of the DoD. Note that formal conference material scanning or other non-published material searching was not conducted as part of this effort. All article bibliographies were also searched for additional studies worthy of inclusion.

The automated search consisted of digital databases using University of Texas Health Science Center San Antonio (UTHSCSA), University of Texas at Austin (UT), and the US Air Force 59th Medical Wing, Wilford Hall Ambulatory Surgical Center (WHASC) library databases, and their inherent database search engines. All of these databases and search terms categories are listed in the table below.

2.2.2.1 Search Parameters

1. Boolean/Phrase search mode

2. No limiting/exclusion terms used in the database search

3. Term: January 1950 through Present (updates received and included as eligible per database through final study database lock time point, January 12, 2017)
Table 3. Databases searched for PIHL literature

<table>
<thead>
<tr>
<th>Databases</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBSCO host: Academic Search Complete (searched the following databases: CINAHL® Plus with Full Text, PsycINFO, Mil&amp;Gov Coll, Agricola, eBook Coll)</td>
</tr>
<tr>
<td>PubMed</td>
</tr>
<tr>
<td>Cochrane Library</td>
</tr>
<tr>
<td>ClinicalTrials.gov</td>
</tr>
</tbody>
</table>

Searches were tracked by date with corresponding files of search history and saved to conduct update searches.

2.2.3 Documentation of each database searched

The current search strategy for PubMed, developed with the assistance of a health sciences librarian experienced in developing search strategies for systematic reviews, was translated and executed across databases. All citations found were imported into RefWorks (ProQuest) to store and check for duplicate citations. After screening out duplicates within each database and between databases, visually verifying duplicates that RefWorks identified as such were in fact duplicate articles, the final number of articles to be screened by title and abstract was transferred into an Excel workbook designed specifically for systematic reviews including blind title/abstract review and decision tracking (VonVille, 2015). Hand-searched, bibliography, and search update garnered articles were all added to
the same database for final article count and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart development (Moher et al., 2009).

2.2.4 Limitations of the Search

This search effort does not include personal outreach to authors. The intent was specifically to determine what the literature would return since that is most often the basis for reference in study design choices. The search also does not include “grey” nor more robustly international, non-English literature. Finally, the search, data extraction and analysis was carried out in full by one reviewer, although efforts were made to ensure inclusion/exclusion reliability with a second reviewer for a sample subset, as discussed in section 2.2.5 below.

Any confusion within or lack of reporting as noted against CONSORT (for clinical trials) or ARRIVE (for animal studies) standards and guidance was not quantitatively recorded or analyzed within an article’s record. Reasons for this were two-fold. First, most clinical trials were not up to Randomized Controlled Trials level of rigor and thus not particularly relevant to CONSORT guidelines. Second, reporting was generally so poor in the quality and documenting of relevant data points, that a full quantitative detail and assessment was not deemed valuable at this time. Instead, those primary data extraction elements which point to the quality of either the study or the quality of reporting will be discussed in Chapter 3, “Results” as an overall commentary on the state of quality studies and reporting in this field. The hope therein is that such a note will spark discussion,
awareness, and change among investigators and authors so that future assessments could be taken on targeting more specific areas for improvement than “overall.”

### 2.2.5 Study Selection Procedures

A preliminary review of title and abstracts was conducted by two reviewers. The primary reviewer and PI on this study (TH) has over 11 years of experience in this field as a research administrator for the HCE where she leads the PIHL group of over 175 experts in the field, as discussed in the literature review above. The secondary reviewer (CE) is a medical doctor (neurotology head-neck surgeon) with over 30 years of experience, also at the HCE, a member of the PIHL group, and advisor to the dissertation project.

To ensure exclusions and eligibility criteria were well-conceived and mutually understood, the primary and secondary reviewers independently reviewed 100 randomly selected titles and abstracts, citing one of the exclusion criteria in Table 4 below for each article recommended for exclusion. Results of the independent review of titles and abstracts returned a Cohen’s kappa score of .91, indicating a high degree of inter-rater reliability (McHugh 2012), and thus no further revisions to exclusion criteria were made. All screening activities were recorded in the Excel Workbooks for Systematic Reviews developed by Helena E. VonVille, including the Primary and Calculate Cohen’s kappa for Screener Inter-rater Reliability workbooks (VonVille 2015).
Table 4. Exclusion Criteria for Screening

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Primary target for intervention is not noise-induced hearing/peripheral tinnitus</td>
</tr>
<tr>
<td>2</td>
<td>Intervention is not a chemical agent</td>
</tr>
<tr>
<td>3</td>
<td>Other auditory conditions (congenital deafness, presbycusis, sudden sensorineural, Meniere's, etc.)</td>
</tr>
<tr>
<td>4</td>
<td>Regeneration study</td>
</tr>
<tr>
<td>5</td>
<td>Not original, cohort, prospective research (review, retrospective, etc.)</td>
</tr>
<tr>
<td>6</td>
<td>Not an in vivo study</td>
</tr>
<tr>
<td>7</td>
<td>Not an intervention study (includes pathophysiology/etiology, delivery or diagnostic approaches, aim to cause HL without intervening to prevent/rescue HL)</td>
</tr>
<tr>
<td>8</td>
<td>Other</td>
</tr>
</tbody>
</table>

2.2.6 Data Collection: Coding

This project employed a single-reviewer coding strategy for all studies. Using Codebook instructions (see Appendix X, Codebook_PIHL_SR), coder entered data directly into the Access database created for the study. Data captured included eight (8) categories of information, with a ninth category available in the codebook for future research efforts (Quality):

1. Citation (C)
2. Study (S), with additional categories specific to:
2.2.7 Intervention Arms

Because of the high level of variability in study arm designs, the coder identified each exposure type employed and measure utilized, and then matched those up per intervention arm with the specific drug administration protocol used in that arm. This allowed analysis of the various combinations of these three variable categories (E, M and D) created across studies. Reporting quality was noted among primary variables (i.e., when elements were not reported, “NR” was captured for quantitative assessment), but also subjectively assessed for general trends. All coded data, collected in MS Access, was exported into separate MS Excel® (2013) tabs and compared for compliance to the study aims and codebook instructions when finalizing (i.e., correcting typos and syntax) the closed data set. All final coded data was transferred into SAS software (v9.4; Cary, NC) database for additional analysis.
2.3 ANALYSIS

Data was imported into Excel or SAS software for analysis. Assessments were primarily comprised of descriptive statistics among the categories of methodology descriptors listed in the data collection coding description above. Assessment for trends of correlation between any exposure categories and other “demographic” categories of the studies, including in vivo models, drug pathway/mechanism, drug delivery method or class, study year or country of study execution categories, was made. The quality and comparability of outcomes reported did not enable any meta-analysis.

Study variables were coded and entered into Access, exported to Excel for data cleaning and organizational preparation for analysis, then imported into SAS statistical software to perform descriptive statistics. Subgroup analyses among like studies (e.g., within human studies for noise exposed population) were conducted to identify, evaluate and summarize any trends of correlation between methodologies utilized in study designs. Previous inquiries by the author and colleagues have found that PIHL study heterogeneity is too great to allow for meta-analysis of outcomes of PIHL drugs. Lack of information reported was also considered a variable of this study.
Table 5. Correlation assessment matrix of variables

<table>
<thead>
<tr>
<th></th>
<th>Citation (C)</th>
<th>Study Design (SA or SC)</th>
<th>Exposure (E)</th>
<th>Drug/Biologic (D)</th>
<th>Measures (M)</th>
<th>Intervention Arm (I)</th>
<th>Outcome (O)</th>
<th>Analytics (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citation (C)</td>
<td>D</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Study Design (SA or SC)</td>
<td></td>
<td>D</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Exposure (NE or OE)</td>
<td></td>
<td></td>
<td>D</td>
<td>C</td>
<td>C</td>
<td>N/A</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Drug/Biologic (D)</td>
<td></td>
<td></td>
<td>D</td>
<td>C</td>
<td>N/A</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Measures (M)</td>
<td></td>
<td></td>
<td></td>
<td>D</td>
<td>N/A</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Intervention Arm (I)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Outcome (O)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D</td>
<td>C</td>
</tr>
<tr>
<td>Analytics (A)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D</td>
</tr>
</tbody>
</table>

“D”=descriptive statistics, “C”=correlation statistics that may be possible.

2.4 TRANSLATION ACTIVITIES – PRIMARY AIM 2

Unlike most systematic reviews, the end-goal for this project is not to simply publish a paper summarizing results with discussion points and recommendations for clinicians to consider during their daily clinical practice decision-making. Rather, the goal
of this review is to create an evidence-base to use as one among several influence tactics in a multi-directional approach aiming to design a new paradigm of translational science termed “BRPs.” These BRPs are intended for investigator adoption with the simple goal of improving the quality and efficiency of the science. However, achieving that goal will equate to different successes to different stakeholders. To the research sponsors, it will mean less cost to translate a product through their portfolio from concept to market. To the journal editors, it will mean higher caliber articles printed in their publications. To the regulatory bodies, it will mean more standardization and thus higher quality and consistency of research approved. To the investigators, it will mean studies with better chances of being funded and published, thus progressing their academic or industry career goals. To be successful with this goal, the PIHL effort must attempt to influence these groups of stakeholders in tailored ways.

Currently, the PIHL group employs a variety of influence tactics across several lanes. Convincing the small community of funding program managers through a combination of ingratiation and inspiration, lobbying efforts are underway to ensure the BRPs are followed in future funded projects. The task of convincing journal editors to advocate for these BRPs is being carried out through special issue publications, which are a draw to new readership. The special issue initiatives are a large undertaking, requiring the coordination of dozens of authors, topic selection, guest editorial boards, etc., yet they provide an opportunity to forge relationships with the journals themselves, and bring the PIHL mission for adoption of these BRPs to their attention. The relationships created can
be the entry point to future suggestions for new policies on publication acceptance, once enough time has passed to allow for the use of disseminated BRPs to permeate practice. Similarly, communication and collaboration with the FDA as a coalition partner in the Federal landscape will continue. And if successful on all of these fronts, an appeal to investigators that if they want to be competitive for grant funding, if they want to minimize publication rejections and revisions, or streamline approvals by the FDA, all they need to do is follow these easy-to-follow BRPs ought to be successful, also known as an “exchange influence tactic” in change management theory (Barry & Shapiro, 1992).

2.4.1 Approach

2.4.1.1 Hypothesis

A strong evidence base, if properly developed and adopted across stakeholders groups, can provide a research roadmap for investigators to follow that can facilitate and improve quality of scientific progress.

2.4.1.2 Rationale

The typical pathway of scientific progress is riddled with inefficiencies and missteps, largely brought about by poor communication and increasingly indigestible amounts of information. Moreover, largely diverse groups of stakeholders are interdisciplinary and thus are not commonly exposed to conference proceedings and publications relevant to their research.
2.4.1.3 Preliminary Studies

As detailed above, this is a novel systematic review for the PIHL field. While the James Lind Alliance's approach to determining appropriate tinnitus outcome measures aligns well with one of the objectives in the systematic review of Aim 1, only the Action on Hearing Loss’s TRIH has comparators to the efforts and goals in Aim 2. However, no literature was found that mimics this trajectory for Aim 2 translational work.

2.4.1.4 Dissemination & Implementation

Upon completion of the systematic review described above, results will be translated into various formats to target stakeholder groups, to include professional conference abstracts for podium and poster presentations, reports and guidance sheets to Federal funding agencies to use as reference, PIHL Newsletter article(s), peer-reviewed journal articles, and briefings for FDA consideration and discussion.
Chapter 3: Results – Primary Aim 1

This chapter will detail the results of the systematic review in three main sections. The first section will describe the literature review results themselves, including search elements included summarized as a PRISMA-style table. The second section will share descriptive statistics and summary tables of the extracted data from the final included set of articles from each data collection section detailed in Chapter 2 above; namely, Citation, Study populations, Exposures, Measures, Drugs, Intervention Arms, Analysis, and Outcomes. Deeper dives into the dataset and “next steps” BRPs will be discussed in the third section.
3.1 Literature Review Results

As detailed in the PRISMA table below, 3,492 articles were returned in the Boolean search of PubMed and CINAHL® Plus with Full Text, PsycINFO, Mil&Gov Collection, Agricola, and eBook Collection with unlimited dates through Oct 09, 2016. An additional 54 articles were found in hand-searches, bibliographies, as well as a second original search extending through January 12, 2017, for a total of 3,546 articles. There were 402 duplicates removed by RefWorks and confirmed manually, leaving 3,144 articles to be blind screened, using title and abstract alone. A total of 2,867 articles were removed (see Table 6 for reasons for exclusion) and 277 were reviewed as full text for inclusion. Ultimately, 213 articles were included in the final data extraction and analysis.

Results of gaining additional hand-searched articles is consistent with the Cochrane review, “Hand-searching versus electronic searching to identify reports of randomized trials,” which showed a much higher rate of return for hand-searching (92% to 100% of the total number of reports included) than electronic searches (which yielded 49%-67%) (Hopewell et al., 2007). The authors rightfully concluded “that a combination of hand-searching and electronic searching is the most comprehensive approach in identifying reports of randomized trials.”

Studies included are detailed in the evidence table provide in Appendix D. The final data set was exported into Excel first to be cleaned (manually ensuring consistent terminology, capitalization, etc. are used throughout) and will be made available to the
PIHL group in that format for ease of transfer and compatibility across systems and preferred statistical packages.
Table 6. PRISMA Table

<table>
<thead>
<tr>
<th>Records found through database searching</th>
<th>Records found through other sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of items identified from database searches</td>
<td># of additional items found outside of database searches to be screened for inclusion</td>
</tr>
<tr>
<td>k = 3492</td>
<td>k = 54</td>
</tr>
</tbody>
</table>

3546 records identified from all sources

402 Internal & external duplicate citations excluded

titles & abstracts
3144 screened

2805 titles/abstracts excluded

217 Primary target for intervention is not noise-induced hearing or peripheral tinnitus
Intervention is not a chemical agent
(acupuncture or devices such as hearing aids or middle- or inner-ear implants)

9 Other auditory conditions (ototoxicity, congenital deafness, presbycusis, sudden sensorineural, Meniere's, etc.)

16 Regeneration study

212 Not original, cohort, prospective research (review, retrospective, case report, etc.)

24 Not an in vivo study

429 Other pathophysiologyletiology, genetics, delivery or diagnostic approaches

573 Other

64 full text articles excluded

20 Primary target for intervention is not noise-induced hearing or peripheral tinnitus
Intervention is not a chemical agent
(acupuncture or devices such as hearing aids or middle- or inner-ear implants)

1 Other auditory conditions (ototoxicity, congenital deafness, presbycusis, sudden sensorineural, Meniere's, etc.)

1 Regeneration study

23 Not original, cohort, prospective research (review, retrospective, case report, etc.)

0 Not an in vivo study

10 Other pathophysiologyletiology, genetics, delivery or diagnostic approaches

0 Other

279 full text records to be reviewed

2 records not available for review

277 full text records reviewed

213 publications included

Reporting on 213 studies
3.2 STUDY CHARACTERISTICS

Of the 213 articles (k = 213) included, two function as doubles in that they had both human and animal experiments and thus descriptive analyses provided reference the 31 human studies and 184 animal studies for a misleading total of 215. While one or two studies were performed at a biennial rate throughout the 1980’s and 1990’s, major interest swelled in the 200’s and continues to steadily increase today, as depicted in Figure 4 below.

![Growth of Publications Over Time](image)

**Figure 4. Human and animal publications by year**

Studies were published in 80 unique journals between 1977 and 2016, with Hearing Research and Acta Oto-Laryngologica responsible for a combined 26% of total included publications.
Sponsors of PIHL research are just as diverse. While 153 studies reported a single source of funding, 45 shared dual funding, and 8 studies had three or more funding sources. With 271 funding sponsor acknowledgements total, foreign governments contributed to 80 studies while the US government funded only 55. The remaining funding came primarily from industry and non-governmental organizations (i.e., foundations) sponsors, though attributions to private universities and hospital systems were not uncommon (see Figure 6). Interestingly, 41 articles did not report any source of funding nor acknowledge that no
funding was required for the study. Given the publication date range for these articles spanning 1984-2016, more recent trends toward more transparent attribution of funding cannot be the cause. Some authors are simply continuing to fail to report funding in publications, and some journals are failing to require the acknowledgement of funding prior to publication. Similarly, there was no significant trend limiting this failure of funding reporting to specific journal publications, but rather was found present among most.

Figure 6. Funding sources of PIHL research focused on NIHL
Author affiliations provided in the literature represent 26 different countries. The vast majority are from the United States, but the search strategy limit to English-only articles may have biased this result (Figure 7). The author’s affiliated institutions, as provided in publications, were used to determine geographic location of study sites. When this information was not obvious, internet searches were conducted. Multiple country affiliations per article were grouped as appropriate (i.e., “European” or “Euro-US-Asian”).

Figure 7. Country affiliations per article (multiple countries represented per article did occur).

Most articles do not list details about the authors themselves. Even credentials are scarce. Thus only organizational affiliations could be captured as commonly reported and
included within the publications. Authors were grouped into one of seven types of organizations: 1) otolaryngology or school of medicine, combined into an “ENT/MD” category; 2) hearing clinical or research center of various names (e.g., “Speech, Hearing & Communications Center” or “Sensory Research Center”); 3) a public, occupational, environmental or industrial health focus; 4) pharmacology, toxicology or pathology laboratory or center; 5) statistics or mathematics; 6) the basic sciences, including neurosciences, biology, chemistry, physiology or any combination thereof; and 7) all others. The latter group includes authors affiliated with institutions focused in the following disciplines: Substance abuse, Anesthesiology, Chinese medicine, Dentistry, Diving Medicine, Endocrinology, Gastrology, Genetics, Gerontology, Inflammatory Disease, IT, Mechanical engineering, Military, Nursing, Oncology, Veterinary. The decisions to group like-focused institutions was not in itself a science – i.e., the choice to group those with chemistry affiliations into the basic sciences group while toxicologists and pathology institutions were grouped with pharma-based institutions could be debated – but raw data is available in the database for others to make their own choices with the data.
Only 28 studies did not include any authors from an institution clearly focused in otolaryngology/medicine or hearing specialties (6 of which were human studies), with 159 including the former, 64 including the latter, and 38 including both on the team. Perhaps more interesting, given the complexities of auditory research variables discussed in greater detail in the following sections, only 11 studies included an author with a specific affiliation to a statistics-focused institution or department.

### 3.2.1 Study Sample Sizes

It was noted that 31 studies did not identify (outright or in the form of clear group delineations) the sample pool used and 19 studies did not report the total number of subjects included for analysis in any way. Many studies did not clearly report either with outright statements (i.e., "15 animals were used in this study," or "15 animals were included in final data analysis"). Generally, detective work was required to piece together groups described
in methods sections for a sample size and then again using results section descriptions or, also too often, graph legends to determine N of analyzed groups.

Within the rest of the articles with both reported sample and analysis group sizes, poor reporting remained evident in 21 articles where the sample size was higher or lower than the reported analysis N without any explanation or acknowledgement of the discrepancy. Most puzzling of all, 6 of these 21 articles reported higher analysis N than the reported sample size. There were another 6 articles which also had discrepancies in before/after sample sizes, but these authors provided adequate reporting of what had occurred, and they were always lower in the end (i.e., attrition in human studies (k=4) or animal death or exclusionary co-morbidity in animal studies (k=2)).

In general (ignoring non-report, unconfirmed/indeterminate studies), human studies ranged from 11 (Suckfuell et al., 2007) to 331 participants (Probst et al., 1992), with an average of 68 (SD of 71), with no particular dependent variable found using regression analysis. None of the factors, including study design (well-controlled, randomized trial versus exploratory study), target indication (prophylaxis versus rescue), country of author affiliation, measures used, number of intervention arms, nor drug variables (drug, dosage, administration route), showed any correlation to study sample sizes. Animal studies varied just as widely, ranging from 6 animals (Takemoto et al., 2004) to 400 (Rewerska et al., 2013), with an average of 54 (SD 55.15), highly dependent on the number of arms used per study. This is not surprising, given that animal studies afford the ability to harvest cochlea for morphological and immunohistochemical analyses, which
require large numbers of animals when various time points and staining mechanisms are utilized.

The same end-of-life tests created a large variety in group sizes and in fact made the definition and quantification of group sizes quite challenging – most studies described a reasonable number of study arms (i.e., < 10), to test obvious primary aims (i.e., 3 different dosing regimens against a control, for a total of 4 arms), yet actually had anywhere between 1 and 38 variations among unnamed groups (for a total entry of 1,667 interventions across the 213 studies). While this was most often due to the variations in measures alone, and is discussed further in section 3.4 below, simple lack of detailed reporting was also a major contributing factor to the inability to accurately define group sizes. A lesson learned that can be applied toward BPRs is the resulting perspective that specific and clear descriptions of groups matter for understanding a study design, and thus the probability of reproducing results, as well as basic ability to interpret results.

3.3 SPECIES

There was not a large variety of animal species used in literature included in this study. Excluding humans and 1 minnow study, all animals were from the rodent genus (see Figure 7). No higher-order mammal studies were found. The chinchilla has a higher degree of similarity to human cochlear anatomy and hearing range and the species reportedly shows an absence of age-related hearing loss (see reviews in Turner et al., 2005 or Clifford et al., 2011), yet both guinea pigs and chinchillas are both subject to higher regulatory oversight and thus increase administrative difficulty and additional vivarium requirements
to a study with their use (Lynch et al., 2016). This has led to a debate in whether PIHL studies ought to be carried out in the popular, cheaper guinea pig, rator mouse models. Use of small rodents undoubtedly serve a purpose in more exploratory work where higher numbers of animals (i.e., multiple morphological cohorts used) or more strictly controlled genetic mutations (i.e., knock-out strains) are required.

Figure 9. Species Across PIHL Noise Studies

Human study authors did a poor job overall of providing subject characteristics. The 2010 CONSORT checklist for reporting randomized trials represents the highest level of reporting standards. Granted, most of the studies presented were not highly controlled, randomized trials (itself a difficult assessment to make given lack of reporting – 7 studies had no controls and 4 used a non-placebo control (i.e., standard of care); 6 did not mention blinding and another 7 reported no blinding design; and roughly half of human studies either did not utilize, mention or adequately report a randomization scheme); nevertheless,
reporting still could easily have included the typical participant characteristics table of information, including ages, weight/BMI, race, ethnicity, socio-economic status, etc. Instead, ethnicity was reported in three studies, weight or BMI in two studies, race in one study, and SES hinted at with description of military status. Only age was consistently reported in all but two human studies.

Animal study authors did a better job reporting animal characteristics, but still failed to meet ARRIVE guidelines for reporting age and weight. Instead, authors more often chose to report one or the other. From the pie charts below (Figures 10, A & B), one can see that authors are relatively consistently poor at reporting both age and weight across continents, and thus there was no author origin affiliation with preference for which of these key elements to omit. In fact, the distribution is similar to general author origins across all studies (Figure 10, C).

![Figure 10, panels A-C. Animal reporting quality by country.](image)
Why are such discrepancies in reporting a problem? Investigating reasons for possible failures to translate positive animal outcomes to clinical efficacy may lead in many directions. If the PIHL group decides to perform deep analysis on possible issues with drug absorption or age confounders, for example, access to consistent information across studies would be vital.

Of interest, particularly with increased attention from all U.S. federal funding agencies on differences between the sexes, the use of male versus female subjects was, expectedly, lopsided. Human studies enrolling patients in a clinic setting may expect to have a more even mix, but the use of several military populations tilted the balance toward more all- or mostly-male participant pools (Lin et al., 2010; Kopke et al., 2015; Xiong et al., 2011a; Lindblad et al., 2011; Psillas et al., 2008; Attias et al., 1994; Le Prell et al., 2011b; Pilgramm et al., 1985; Hoffer et al., 2013; Markou et al., 2001; Markou et al., 2004). Conversely, animal studies often referenced the articles which discuss the differences between male and female responses to noise exposure (McFadden et al., 1999; El Barbary et al., 1993; Julicher et al., 1984) and thus chose all of one sex for their study. As Table 7 shows, not all studies took this route, and not all did so blindly. Many of the animal studies with an even mixture did so while quoting the same sorts of studies regarding different morphology, damage risk patterns, ROS detoxification ability, etc. (as did Landegger et al., 2016 as well as McFadden et al., 2005, as examples), to also examine such difference
further in their own studies. Of course, there were also many studies in which the selection of all versus mixtures of sexes was not acknowledged at all.

Table 7. The numbers of participants per study overall, per human study, and per animal study, respectively.

<table>
<thead>
<tr>
<th>Overall</th>
<th>Human</th>
<th>Animal</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Female</td>
<td>30 (14.1%)</td>
<td>All Female</td>
</tr>
<tr>
<td>All Male</td>
<td>92 (43.2%)</td>
<td>All Male</td>
</tr>
<tr>
<td>Mostly Male (&gt;70%)</td>
<td>10 (4.7%)</td>
<td>Mostly Male (&gt;70%)</td>
</tr>
<tr>
<td>Even mix</td>
<td>24 (11.3%)</td>
<td>Even mix</td>
</tr>
<tr>
<td>Not reported</td>
<td>57 (26.8%)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

One notable distinction among studies in regards to gender of the animals is seen in Figure 11, where small rodent models were overwhelmingly all-male, while guinea pigs had a broader distribution and chinchillas were more predominantly tested in female cohorts.
Figure 11. Distribution of gender per animal species

Just as interest within the PIHL Group is peaked for differences among the sexes (Mitra et al., 2017), so to interest in the effect of animal strain and breeder variety on intervention outcomes is growing (Whitlon et al., 2017). Possible effects on outcomes can be investigated further using this database as a launchpad when such details were reported, which they were in 91% of animal studies. Those not reporting strain or breeder primarily came from chinchilla studies ($k=15$), and 3 guinea pig studies not reporting. While that seems promising, many reports of animal strain were purely descriptive (e.g., “pigmented” versus “albino”, although one article reported the former in the abstract and the latter in the text, so quality issues persist in this field as well). Authors often stop short of providing useful details for assessing all differences possible among animals used, including breeder information (Whitlon, 2017), the latter reported in only 50% of studies included herein.
3.4 Exposures

3.4.1 Noise Exposures

With seven studies using multiple types of noise exposure (Bielefeld et al., 2007; Bielefeld, 2013; Franze et al., 2003; Harris et al., 2005; Hight et al., 2003; Kopke et al., 2015; Zhou et al., 2013), there are 220 records of noise exposure types utilized across the 213 studies. Interestingly, the two articles with both human and animal cohorts were NOT among those seven and instead exposed all subjects to the same noise exposures (Jogelkar et al., 1977; Witter et al., 1980). With a variety of descriptive choices, all 220 were grouped into the eight categories displayed in Table 8 below, with broad band making up the vast majority (k=124), followed by impulse noise studies (k=38). Blast studies were conducted four times, 3 of which were in animal models for obvious reasons; namely, conducting a blast study in humans would be extremely difficult given logistical (access, timing, etc.) and co-morbidity/mortality (including superseding intervention requirements) challenges. The one exception to this is the Kopke et al. (2015) clinical trial in U.S. Marine Corps recruits who experienced a primary noise insult from 16 days of weapons training with rifles. However, they also experienced a week of “hell week” in which mortars and grenades are experienced in close proximity and thus there were chances for mild blast exposures in this cohort.
Table 8. Noise Types Utilized in Study Designs (k=213)

<table>
<thead>
<tr>
<th>TOTALS</th>
<th>k=</th>
<th>k=</th>
<th>k=</th>
<th>k=</th>
<th>k=</th>
<th>k=</th>
<th>k=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad Band</td>
<td>124</td>
<td>Single Pure Tone</td>
<td>22</td>
<td>Narrow Band</td>
<td>10</td>
<td>Mixed / Other</td>
<td>9</td>
</tr>
<tr>
<td>Octave Band</td>
<td>62</td>
<td>10 kHz Pure Tone</td>
<td>4</td>
<td>Narrow band</td>
<td>7</td>
<td>Mixed</td>
<td>3</td>
</tr>
<tr>
<td>White noise</td>
<td>23</td>
<td>6 kHz Pure Tone</td>
<td>4 kHz narrow band</td>
<td>Military</td>
<td>2</td>
<td>mixed</td>
<td>2</td>
</tr>
<tr>
<td>Broad band</td>
<td>21</td>
<td>4 kHz Pure Tone</td>
<td>6</td>
<td>Band-limited</td>
<td>1</td>
<td>&quot;Other&quot;</td>
<td>2</td>
</tr>
<tr>
<td>Pure Tone/</td>
<td>11</td>
<td>2 kHz Pure Tone</td>
<td>Violet swept sine (VS)</td>
<td>1</td>
<td>Kurtotic</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Broadband</td>
<td>3</td>
<td>1 kHz Pure Tone</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White band</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wide band</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Band noise</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the interest of determining optimal translational strategies, the more important data to track will be the comparisons between the noise insults utilized in the laboratory settings versus clinical trials, and ultimately, real world noise hazard scenarios in which PIHL agents are intended to intervene. Figure 14 below shows the side-by-side comparison of noise types used in included studies. The ethical restrictions on inflicting a noise injury on human study volunteers will likely keep the broadband noise category low for human studies, while military and recreational (i.e., music venues) opportunities to study people who would otherwise be subject to the noise hazards, is likely going to grow the impulse, occupational, and mixed categories over time. Such real-world scenarios are more difficult and costly to simulate in a preclinical model, and thus, the divide between types of noise exposures studied in animals and humans are likely to continue, but awareness and acknowledgement of the need to examine possible repercussions on study outcomes must be constant.
Figure 12. Noise types by animal vs. human studies

There were 34 articles in total that had multiple arms of noise exposure elements, distinguished by type, already discussed above, sound levels, exposure durations or numbers of exposures, or, in one case, the time of day (see Table 9). The aim to test drug efficacy against various damage exposures did not always follow a clearly logical pathway. One early thought upon starting this systematic review was to document a “reference tree” – a chain of references listed for choices made in noise exposure study design. However, so often there were no such references provided that such a record became obsolete in the pilot phase of the effort. Instead, the information collected by this review can be used by the PIHL group of SMEs to determine if any noise exposures used are indeed the “most appropriate” for particular damage pathways intended, by species.

The only study which included multiple species within experiments (other than the two human-animal studies mentioned above) also included multiple noise arms
(Frederiksen et al., 2007), with the stated aim to “investigate…three different modes of drug application, different administration time windows and different rodent species,” without mention that unique sound levels were also built in to the study design. Needless to say, one study with such high variability is not enough to determine best practices. Instead, efforts will be required of the PIHL group animal and sound committee SMEs to combine evidence provided herein with the body of literature that abounds on noise effects in each particular rodent species.

Table 9. Articles with a multiple noise cohorts.

<table>
<thead>
<tr>
<th>Article ID</th>
<th>Type</th>
<th>Sound Level</th>
<th>Exposure Duration</th>
<th>Number of Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adelman et al. (2011)</td>
<td>Simulated vs actual rifle fire</td>
<td>123, 135, 155 dB SPL</td>
<td></td>
<td>10, 120, 700</td>
</tr>
<tr>
<td>Bielefeld (2013)</td>
<td>Impulse vs Octave band</td>
<td>155 vs 106 dB SPL, respectively</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bielefeld et al. (2007)</td>
<td>Octave Band vs Kurtotic/mixed vs. Impulse</td>
<td>105, 123, 155 dB SPL, respectively</td>
<td>6 hrs, 2 hrs, 2 seconds, respectively</td>
<td>150 impulses</td>
</tr>
<tr>
<td>Bielefeld et al. (2011b)</td>
<td></td>
<td>107 vs 112 dB SPL</td>
<td>2 hrs and 4 hrs, respectively</td>
<td></td>
</tr>
<tr>
<td>Chang et al. (2016)</td>
<td></td>
<td>110, 120 dB SPL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chaturvedi et al. (1988)</td>
<td></td>
<td></td>
<td></td>
<td>20 or 40 min</td>
</tr>
<tr>
<td>Ewert et al. (2012)</td>
<td></td>
<td>13.7 PSI vs 23 PSI</td>
<td></td>
<td>2, 3 or 4 exposures to 13.7</td>
</tr>
<tr>
<td>Franze et al. (2003)</td>
<td>Impulse vs white band noise</td>
<td>114, 120 dB SPL respectively</td>
<td>2 or 5 hrs in each condition</td>
<td></td>
</tr>
</tbody>
</table>
Table 9 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>SPL Description</th>
<th>Duration Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frederiksen et al. (2007)</td>
<td>105 vs 110 dB SPL</td>
<td>1 8 hr session vs 3 consecutive days of 8 hrs</td>
</tr>
<tr>
<td>Han et al. (2015b)</td>
<td>92, 96, 98 dB SPL</td>
<td></td>
</tr>
<tr>
<td>Harris et al. (2005)</td>
<td>Impulse vs Octave band</td>
<td>155, 106 dB SPL respectively 4 hrs in OB 150 impulses</td>
</tr>
<tr>
<td>Harrop-Jones et al. (2016a)</td>
<td>105 vs 110 dB SPL</td>
<td></td>
</tr>
<tr>
<td>Harrop-Jones et al. (2016b)</td>
<td>105 vs 110 dB SPL</td>
<td></td>
</tr>
<tr>
<td>Henry (1992)</td>
<td>120 vs 122 dB SPL</td>
<td></td>
</tr>
<tr>
<td>Hight et al. (2003)</td>
<td>Impulse vs Octave band</td>
<td>145, 105 dB SPL, respectively 4 hrs in OB 100 impulses</td>
</tr>
<tr>
<td>Hill et al. (2016)</td>
<td>92, 98, 106 dB SPL</td>
<td></td>
</tr>
<tr>
<td>Jogelkar et al. (1977)</td>
<td></td>
<td>1 vs 3 10 min exposures</td>
</tr>
<tr>
<td>Kopke et al. (2015)</td>
<td>Impulse, continuous, blast</td>
<td>3 or 13 days</td>
</tr>
<tr>
<td>Lynch et al. (2004)</td>
<td></td>
<td>110, 113, 115 dB SPL</td>
</tr>
<tr>
<td>Meltser et al. (2014)</td>
<td>Day vs Night exposure</td>
<td></td>
</tr>
<tr>
<td>Mori et al. (2004)</td>
<td>100 vs 120 dB SPL</td>
<td></td>
</tr>
<tr>
<td>Müller et al. (2016)</td>
<td></td>
<td>15, 30, 45, 60, 120 impulses</td>
</tr>
<tr>
<td>Murashita et al. (2006)</td>
<td></td>
<td>110, 120, 128 dB SPL</td>
</tr>
<tr>
<td>Murillo-Cuesta et al. (2015)</td>
<td>100, 110, 120 dB SPL</td>
<td>30 min vs 12 hrs at 100 dB SPL</td>
</tr>
<tr>
<td>Nagashima et al. (2010)</td>
<td></td>
<td>90, 100, 110, 120 dB SPL</td>
</tr>
<tr>
<td>Peppi et al. (2011)</td>
<td>88, 100, 102 dB SPL</td>
<td></td>
</tr>
<tr>
<td>Puel et al. (1998b)</td>
<td>100, 110, 120, 130 dB SPL</td>
<td></td>
</tr>
</tbody>
</table>
The frequencies chosen - again, the results of mostly unreported decisions – varied as much as the exposure times chosen (compare Figures 12 and 13). The use of 4 kHz stood out as the most commonly used not because it was used as a sole pure tone frequency exposure, as Table 9 above confirms only occurred 6 times. Rather, 4 kHz was often referenced as the center frequency in broad band or octave band exposures and, thus, recorded as such. This resulted in the high tick in graphic format. Most other exposures were used in general distribution across frequencies within the range of human hearing of roughly 20 – 20,000 Hz (Turner et al., 2005). The time of exposure variable, however, is quite skewed. The Pearson correlation between dB SPL and log (time of exposure) yields a correlation of $r=-0.197$ with a p-value of $p=0.0037$ for the 215 paired samples. Therefore, sound level is, not surprisingly, inversely related to the time of exposure.

<table>
<thead>
<tr>
<th>Study</th>
<th>Frequency(s)</th>
<th>Exposure Time(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scholik et al. (2004)</td>
<td>2 vs 24 hrs</td>
<td></td>
</tr>
<tr>
<td>Sly et al. (2016)</td>
<td>95 vs 105 dB SPL</td>
<td></td>
</tr>
<tr>
<td>Takahashi et al. (1996)</td>
<td>110, 115, 120 db SPL</td>
<td></td>
</tr>
<tr>
<td>Wang et al. (1999)</td>
<td>100 vs 105 dB SPL</td>
<td></td>
</tr>
<tr>
<td>Witter et al. (1980)</td>
<td>110, 120, 135 db SPL</td>
<td></td>
</tr>
<tr>
<td>Zheng et al. (2014)</td>
<td>92, 98, 106 db SPL</td>
<td></td>
</tr>
<tr>
<td>Zhou et al. (2013)</td>
<td>Fireworks, mixed, other</td>
<td></td>
</tr>
</tbody>
</table>
In addition to the quantifiable variables described above, as much information about sound exposures as possible was also recorded free-field into the database. This information included whether or not animals were anesthetized, the entire speaker system
– from sound file to horn delivery, and all reported pieces between – as well as any other pertinent information to reproducibility of the study design. Overall, authors were comprehensive in the technical setup of the sound delivery in animal studies and details were plentiful and comparable across designs. However, in human studies, where subjects were most often self-reports in clinical settings, details were sparse even when a noise history questionnaire was listed among the data collection. Thus, in the human cohort of data, understanding the noise damage is impossible in most cases. In prospective field studies, sound level measures and noise source descriptions were more common.

3.4.2 Ototoxic Exposures

Only five studies included an ototoxic insult arm in their otherwise NIHL-targeted studies, all unsurprisingly using animal models (Wang et al., 1999; Wang et al., 2003; Rao & Fechter, 2000; Guitton & Dudai, 2007; Pouyatos et al., 2007).

Table 10. Ototoxic Exposure Data

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Name</th>
<th>Type</th>
<th>Dose</th>
<th>Schedule</th>
<th>Duration</th>
<th>Admin/ Route Description</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guitton &amp; Dudai (2007)</td>
<td>salicylate</td>
<td>drug</td>
<td>300 mg/kg</td>
<td>1x between Day 12 and 15</td>
<td>NA</td>
<td>injection OR artificial perilymph soaked gel applied to RWM</td>
<td>induce tinnitus</td>
</tr>
<tr>
<td>Pouyatos et al. (2007)</td>
<td>acrylonitrile</td>
<td>industrial chemical</td>
<td>50 mg/kg s.c. injection</td>
<td>30 min prior to daily NE1</td>
<td>5 days</td>
<td>NR</td>
<td>cause/ potentiate HL</td>
</tr>
<tr>
<td>Rao &amp; Fechter (2000)</td>
<td>carbon monoxide</td>
<td>inhalation chamber</td>
<td>1200 ppm during NE1</td>
<td>02:00 HR</td>
<td>a 90-min CO pre-exposure</td>
<td>NIHL potentiation</td>
<td></td>
</tr>
<tr>
<td>Wang et al. (1999)</td>
<td>carboplatin</td>
<td>drug</td>
<td>75 mg/kg</td>
<td>1x 4 days post Drug admin</td>
<td>NA</td>
<td>1.5 ml</td>
<td>destroy IHCs</td>
</tr>
<tr>
<td>Wang et al. (2003)</td>
<td>neomycin sulfate</td>
<td>drug</td>
<td>300 mg/kg</td>
<td>daily, starting Day 2</td>
<td>5 days</td>
<td>i.p. injections</td>
<td>cause HL</td>
</tr>
</tbody>
</table>
In Guitton et al.’s study using both noise and salicylate insults, the salicylate did a more reliable job of inducing tinnitus (2007). Rao & Fechter, well known for their work in hearing conservation and occupational exposures to noise and ototoxins (see review in Hammill et al., 2017; Fetcher & Rao, 2002), were as concerned with the synergistic effects of carbon monoxide as they were with the prophylactic administration of the antioxidant phenyl-N-tert-butynitrone (PBN) to prevent injury from either (2000). Wang and colleagues looked at anti-apoptotic agents against carboplatin or aminoglycoside versus efficacy against NIHL and found that leupeptin protected against noise but not carboplatin, while the JNK-inhibitor agent applied directly to the scali tympani protected slightly better against neomycin than noise, though the latter was mitigated in dose-dependent manner (Wang et al., 1999, Wang et al., 2003). All of these are interesting peeks into the possible cross-applicability of the most investigated PIHL agents for both NIHL and ototoxicity. Given the frequency with which metabolic pathways common to both indications were referenced in background and discussion sections across this body of literature, it was surprising to find no more than five investigations directly comparing drug intervention against both sources of injury. A calculated dual indication design does offer the possibility to confirm the mechanisms of action for both damage and drug alike.
3.5 MEASURES

Measures are perhaps the most difficult element to adequately describe in this dataset. The sheer variability is overwhelming, with 826 variations across the 213 studies (overall mean 3.88; SD ±2.87; clinical studies mean 4.9; SD ±3.98, range 1-17; animal studies mean 3.69; SD ±2.6, range 1-14). Human subjects have the benefit of providing subjective responses, and so many additional measures are added in the form of questionnaires, as well as the routine clinical trial medical exam measures taken into account. In animals, however, most of that variation comes in the form of data collection at specific time points within each audiological or histological measure, which, in the database schematic used here, equates to unique records. For example, when a study sampled one cohort daily, Days 1 - 7 and another cohort at Day 1 only, the study has two distinct records for ABR measurement. Imagine the variety when animals were sacrificed at 5 different time points but had ABR measures for every possible time point until their time of death. Conversely, some study designs dictated various time points for data collection, such as in studies comparing pre- versus post-exposure treatment paradigms. Animals receiving prophylactic treatment also received earlier measurements compared to their rescue treatment scheduled counterparts. Variations in time points alone were cause for 157 total duplicative records of the 826, affecting 80 studies, with an average of almost 2 duplicates based on time point differences alone per study that used such designs. What does that translate to? In the one human study this applies to, it means that patients were put into different visit timeline cohorts. For animal study design, it most often means that any end-of-life measures (i.e., immunohistochemical or morphological) were often repeated and often required multiple records for adjoining physiological measurements.
Table 11. Duplicated measure records based on unique data collection timepoint paradigms

<table>
<thead>
<tr>
<th>Measures with multiple time points</th>
<th># of duplicates created</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABR</td>
<td>48</td>
</tr>
<tr>
<td>blood sample</td>
<td>2</td>
</tr>
<tr>
<td>CAP</td>
<td>4</td>
</tr>
<tr>
<td>DPOAE</td>
<td>6</td>
</tr>
<tr>
<td>electron spin resonance (ESR)</td>
<td>2</td>
</tr>
<tr>
<td>IC-EVP (evoked potentials)</td>
<td>1</td>
</tr>
<tr>
<td>immunohistochemistry</td>
<td>77</td>
</tr>
<tr>
<td>morphology</td>
<td>12</td>
</tr>
<tr>
<td>water t-maze conditioning</td>
<td>1</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>153</strong></td>
</tr>
</tbody>
</table>

With these duplicates merged into one record per study, overall time points were assessed from the point of Exposure onset (noise or ototoxic), and the resulting general distributions are shown in Figures 15-17 where every time point per measure is included. Some assumptions had to be made in order to graph these figures since data collection of precise time points was often challenging due to reporting quality. Time points described as “immediately after noise exposure” or “between 1 to 7 days prior to noise exposure” required some shifts in the data, made as consistently as possible across studies, in order to produce these summative graphs of measure data collection in relation to exposure times. That said, they provide useful insights about what sort of conclusions can be supported by the outcomes produced using these time points. Clearly, TTS can is consistently determined, but how often is PTS being examined? Are morphological investigations
correlating with functional measures? These underlying datasets can also serve as fodder for those wanting to confirm correlations between human and animal measures further.

Figure 15, panels A & B. The data collection time point distribution for ABR measures in animals and pure tone audiometry in humans, respectively

Figure 16, panels A & B. The data collection time point distribution for otoacoustic emissions measures, in animals and humans, respectively
Figure 17. The data collection time point distribution for immunohistochemistry & morphological measures in animals

What these graphs cannot convey is the average number of data collection time points per study, shown in Table 12. Once the variability is scaled down, by eliminating the duplicates per study, a simple descriptive table of all measures used is helpful in assessing common domains as well as understanding the use of peripheral measures.

Table 12. Primary measure summary and listing of all other measures, respectively

<table>
<thead>
<tr>
<th>Unique Measures</th>
<th>k Animal Studies</th>
<th>k Human Studies</th>
<th># Time Points Per Study (mean ± SD): Animal</th>
<th># Time Points Per Study (mean ± SD): Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABR</td>
<td>145</td>
<td>1</td>
<td>3.7 ±1.6 SD</td>
<td>3</td>
</tr>
<tr>
<td>Bloodflow</td>
<td>6</td>
<td>1</td>
<td>1.5 ±0.8</td>
<td>3</td>
</tr>
<tr>
<td>Bloodwork</td>
<td>10</td>
<td>9</td>
<td>3.18 ±3.3</td>
<td>3.1 ±2.4</td>
</tr>
<tr>
<td>PTA (incl. bone PTA)</td>
<td>0</td>
<td>31</td>
<td>n/a</td>
<td>5.8 ±3.8</td>
</tr>
<tr>
<td>CAP</td>
<td>22</td>
<td>0</td>
<td>3.3 ±3.0</td>
<td>n/a</td>
</tr>
<tr>
<td>CM</td>
<td>3</td>
<td>0</td>
<td>2.67 ±2.1</td>
<td>n/a</td>
</tr>
<tr>
<td>Genetic Tests</td>
<td>24</td>
<td>1</td>
<td>1.3 ±1.0</td>
<td>1</td>
</tr>
<tr>
<td>Histo/Morph*</td>
<td>122</td>
<td>0</td>
<td>1.1 ±0.4SD</td>
<td>n/a</td>
</tr>
<tr>
<td>Immunohistochemistry*</td>
<td>73</td>
<td>0</td>
<td>2.1 ±1.8 SD</td>
<td>n/a</td>
</tr>
<tr>
<td>OAEs</td>
<td>35</td>
<td>8</td>
<td>5.3 ±3.5 SD</td>
<td>3.6 ±1.5 SD</td>
</tr>
</tbody>
</table>
Table 12 (continued)

*combined any testing done in these categories, often multiple per study

List of Other Measures:

<table>
<thead>
<tr>
<th>ANIMAL</th>
<th>HUMAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMLR (auditory middle latency responses)</td>
<td>Animal naming test</td>
</tr>
<tr>
<td>Extracellular single neuron recordings in the central nucleus of the inferior colliculus (CNIC)</td>
<td>Bone Conduction</td>
</tr>
<tr>
<td>Gap prepulse inhibition of acoustic startle (GPIAS)</td>
<td>Controlled Oral Word Association Test (COWA)</td>
</tr>
<tr>
<td>Prepulse Inhibition (PPI)</td>
<td>Diary</td>
</tr>
<tr>
<td>Spectrum of the neural noise (SNN)</td>
<td>Dizziness questionnaire</td>
</tr>
<tr>
<td>Water t-maze conditioning paradigm</td>
<td>Drug test</td>
</tr>
<tr>
<td>Otoscopy</td>
<td>Dynamic Gait Index</td>
</tr>
<tr>
<td>Pinna reflex test</td>
<td>ECOC thresholds</td>
</tr>
<tr>
<td>CN Determination</td>
<td>Electronystagmography (ENG)</td>
</tr>
<tr>
<td>Intra-Cochlear Evoked Potentials (IC-EVP)</td>
<td>Head thrust test</td>
</tr>
<tr>
<td>Auditory Evoked Potentials (AEP)</td>
<td>Health history questionnaire</td>
</tr>
<tr>
<td>Acoustic Startle Response</td>
<td>Hearing questionnaire</td>
</tr>
<tr>
<td>Cerebrospinal fluid analysis</td>
<td>Medical history</td>
</tr>
<tr>
<td>Electron spin resonance (ESR)</td>
<td>Minimum masking level (MML)</td>
</tr>
<tr>
<td>Medial olivocochlear efferent terminals (MOC ET)</td>
<td>Noise exposure questionnaire</td>
</tr>
<tr>
<td>Cochlear temperature</td>
<td>Nystagmoscopy/nystagmography</td>
</tr>
<tr>
<td></td>
<td>Otologic exam</td>
</tr>
<tr>
<td></td>
<td>Personal noise measurements</td>
</tr>
<tr>
<td></td>
<td>Physical exam</td>
</tr>
<tr>
<td></td>
<td>Psychoacoustical modulation transfer function (PMTF)</td>
</tr>
<tr>
<td></td>
<td>Question/Answer</td>
</tr>
<tr>
<td></td>
<td>Romberg/tandem Romberg Test</td>
</tr>
<tr>
<td></td>
<td>Speech discrimination</td>
</tr>
<tr>
<td></td>
<td>Structured Interview</td>
</tr>
<tr>
<td></td>
<td>Subjective hearing hearing loss questionnaire</td>
</tr>
<tr>
<td></td>
<td>Tinnitus Handicap Index (THI)</td>
</tr>
<tr>
<td></td>
<td>Tinnitus Severity Index (TSI)</td>
</tr>
<tr>
<td></td>
<td>Tinnitus: Loudness Match</td>
</tr>
</tbody>
</table>

88
Specifically, clinical studies for PIHL agents, not surprisingly, all included the gold standard for audiological testing; namely, pure tone audiometry (PTA). However, because not all studies reported which frequencies were tested, a slightly confusing result comes from graphing the distribution of tones used (see Figure 18A) where it appears that perhaps some investigators decided not to test the 4 kHz frequency in a NIHL study, which would be odd indeed. In fact, all reporting authors did test the 4 kHz frequency, while only 2 studies did not report any frequencies tested.

![Figure 18 (continued below)](image-url)
Returning to the question on how animal ABR test results translate to human behavioral audiometry, the lack of clear correlation here deserves further investigation and insights from the PIHL group. Unfortunately, studies largely do not provide raw data to plug in outcomes and perform any meta-analysis on this topic.

Other human measures used in addition to the gold standard PTA included the general battery of history and physical exam included in most clinical studies. Beyond that, domains of interest appear quite haphazard, from use of otoacoustic emissions, to pharmacokinetics, to collection of noise insult information to tinnitus. However, upon closer inspection by SMEs within the PIHL group, these seemingly haphazard choices may reflect different priorities of investigative teams as well as variations in clinical logistics (i.e., limited time availability of the patients). These questions will require further scrutiny.
Figure 19. Human Study Measures

The 31 studies resulted in 144 unique measure records in all, averaging 4.6 per study. Driving the standard deviation of 3.5 is the use of multiple questionnaires in some but not all studies. Tinnitus in particular was a glaring example of variety in measures. As it has been noted across all tinnitus research (Hall et al., 2016), measures for tinnitus are highly variable. No graph is required to show the distribution of tinnitus questionnaires used in NIHL PIHL studies:
• Tinnitus Handicap Questionnaire (THQ) (k=1)
• Tinnitus questionnaire (k=6)
• Tinnitus Minimum masking level (MML) (k=5)
• Tinnitus annoyance "today" (k=1)
• Tinnitus Annoyance (TAQ) (k=2)
• Tinnitus Handicap Index (THI) (k=2)
• Tinnitus loudness "right now" (k=1)
• Tinnitus Loudness Questionnaire (TLQ) (k=1)
• Tinnitus screener (k=1)
• Tinnitus Severity Index (TSI) (k=1)
• Tinnitus: Loudness Match (k=1)
• Tinnitus: Patient global impression of change (PGIC) (k=2)
• Tinnitus: visual analogue scale (VAS) (k=1)

With 12 of 31 human studies collecting tinnitus measures and using 13 unique metrics among them, it is crystal clear that determinations about tinnitus domains and measures is sorely needed.

While finding an abundance of human tinnitus metrics, suprathreshold and speech-in-noise testing were rarely conducted despite such measures being touted as “useful supplements to the behavioral audiogram for assessment of possible neurodegeneration in noise-exposed listeners,” particularly for clinical trial end points (Le Prell & Brungart, 2016). Although these metrics have been known and recommended since the 1960’s, recent developments in understanding “hidden hearing loss” deficits which are undetected by traditional PTA testing have increased attention on these testing metrics (Kujawa & Liberman, 2009; Le Prell & Lobarinas, 2015). Since this recommendation has been slowly
growing in popularity in only the few most recent years, it is not surprising to see them missing; it is simply worth noting as that discussion continues to evolve.

With the abundance of information collected about all measures across animal and human studies, there is an endless supply of research questions to be answered. Text boxes in the database allowed the capture of various definitions of hearing loss in ABR, PTA, OAE and morphological analysis. Given the variants among definitions used across hearing conservation agencies in the U.S. alone (see review in Campbell et al., 2016), it is no surprise that no single standardized definitions for all or any of these hearing metrics exists for use as pre-clinical or clinical trial end points. But those, among many other questions, will be prime targets for team of SMEs within the PIHL group to take on in future work.
3.6 DRUGS

The variety of drug variables comes largely in the form of delivery mechanisms, across both the route and mechanism of administration, with 17 general categories of latter and 12 of the former, as follows:

Mechanisms of Administration:

- aerosol-mediated
- diffusion
- dissolved in drink
- feed
- gavage or feeding tube
- gelatin sponge or hydrogels
- gelfoam/gelfoam pledges
- hyaluronic acid gel
- infusion/perfusion (ampoule, cannula, catheter, centrifuse tube, glass pipette, microcatheter/ osmotic pump)
- inhalation
- injection
- instilled
- micro medical tube
- microsyringe injection
- nanoparticles
- sonde/probe
- tablets (chewable, effervescent, whole)

Routes of Administration:

- intracochlear
- intragastric
- intramuscular
- intraperilymph
- intraperintoneal
- intratympanic
- intravenous
• oral
• pulmonary
• Round window membrane (RWM)
• scala tympani
• subcutaneous

Removing placebo and control agents, there are 704 records for unique drug administration which may include variances in drug itself, dosage, dose schedule, mechanism or site of administration. Further cleaning the dataset to remove all duplicate records for variants other than drug itself (i.e., duplicates caused by the mechanisms listed above or dosing variants), the data hold 227 unique chemical agents, representing 134 drug classes, targeting 37 different mechanisms of action through 6 modalities – biologics, dietary supplements, oxygenating gases, gene therapy, nutriceuticals, and small molecules. Considering there are 213 articles, 227 unique non-placebo agents equates to many studies (90, or 42% to be exact) designed to test multiple agents. Antioxidant cocktails make up a lot of these, but so too do studies investigating any class of drug which uses a steroid control treatment group, which occurred frequently. While Table 14 details individual drugs (counted only once per study despite other variants), an alternative count method confirmed that, after anti-oxidants, corticosteroids were the next most common drug class investigated (in 49 versus 42 studies, respectively).

Table 13. Full list of chemical agents in order of highest frequency investigated (abbreviated, see glossary for full names).

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action</th>
<th>Drug Class</th>
<th>k</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAC</td>
<td>anti-oxidant</td>
<td>Amino acid derivative</td>
<td>25</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>anti-inflammatory</td>
<td>Corticosteroid</td>
<td>14</td>
</tr>
<tr>
<td>methylprednisolone</td>
<td>anti-inflammatory</td>
<td>Corticosteroid</td>
<td>14</td>
</tr>
<tr>
<td>Substance</td>
<td>Action</td>
<td>Classification</td>
<td>Effect</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------------------------------------</td>
<td>----------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Mg</td>
<td>Increased cochlear blood flow; anti-apoptotic</td>
<td>Mineral</td>
<td>Mixture of oxygen and carbon dioxide gas (usually 70/30)</td>
</tr>
<tr>
<td>carbogen</td>
<td>Increased cochlear blood flow</td>
<td>Oxygen/CO2</td>
<td>8</td>
</tr>
<tr>
<td>D-met</td>
<td>Anti-oxidant</td>
<td>Amino acid derivative</td>
<td>8</td>
</tr>
<tr>
<td>ALCAR</td>
<td>Anti-oxidant</td>
<td>Amino acid derivative</td>
<td>7</td>
</tr>
<tr>
<td>predisolone</td>
<td>Anti-inflammatory</td>
<td>Corticosteroid</td>
<td>6</td>
</tr>
<tr>
<td>4-OHPBN</td>
<td>Anti-oxidant</td>
<td>Spin trapping agent</td>
<td>5</td>
</tr>
<tr>
<td>L-NAC</td>
<td>Anti-oxidant</td>
<td>Amino acid derivative</td>
<td>5</td>
</tr>
<tr>
<td>α-tocopherol</td>
<td>Anti-oxidant</td>
<td>Vitamin E</td>
<td>5</td>
</tr>
<tr>
<td>AM-101</td>
<td>Anti-excitatory</td>
<td>NMDA receptor antagonist</td>
<td>4</td>
</tr>
<tr>
<td>ascorbic acid</td>
<td>Anti-oxidant</td>
<td>Vitamin C</td>
<td>4</td>
</tr>
<tr>
<td>ebselen</td>
<td>Anti-oxidant</td>
<td>Glutathione peroxidase mimetic</td>
<td>4</td>
</tr>
<tr>
<td>furosemide</td>
<td>Anti-excitatory (suppresses auditory neuronal activity, but it also inherently ototoxic)</td>
<td>Loop diuretic</td>
<td>4</td>
</tr>
<tr>
<td>HBO</td>
<td>Increased cochlear oxygen</td>
<td>Hyperbaric oxygen</td>
<td>4</td>
</tr>
<tr>
<td>L-NAME</td>
<td>Anti-oxidant</td>
<td>Nitric oxide synthase (NOS) inhibitor</td>
<td>4</td>
</tr>
<tr>
<td>pentoxifylline</td>
<td>Increased cochlear blood flow</td>
<td>Blood viscosity reducer</td>
<td>4</td>
</tr>
<tr>
<td>salicylate</td>
<td>Anti-inflammatory</td>
<td>Non-steroidal anti-inflammatory</td>
<td>4</td>
</tr>
<tr>
<td>tempol</td>
<td>Anti-oxidant</td>
<td>Spin trapping agent</td>
<td>4</td>
</tr>
<tr>
<td>Tempol</td>
<td>Anti-apoptotic, anti-oxidant</td>
<td>Superoxide dismutase mimetic</td>
<td>4</td>
</tr>
<tr>
<td>AM-111</td>
<td>Anti-apoptotic; anti-inflammatory</td>
<td>JNK inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>edaravone</td>
<td>Anti-oxidant</td>
<td>Free radical scavenger</td>
<td>3</td>
</tr>
<tr>
<td>FA</td>
<td>Anti-oxidant</td>
<td>Phytochemical</td>
<td>3</td>
</tr>
<tr>
<td>idebenone</td>
<td>Anti-oxidant</td>
<td>Metabolic coenzyme analog</td>
<td>3</td>
</tr>
<tr>
<td>KX1-004</td>
<td>Anti-apoptotic</td>
<td>Src inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>mifepristone</td>
<td>n/a (used for testing, not as therapy)</td>
<td>Glucocorticoid receptor (GR) antagonist</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 13 (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect/Action</th>
<th>Category/Function</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q-ter</td>
<td>anti-oxidant</td>
<td>Metabolic coenzyme</td>
<td>3</td>
</tr>
<tr>
<td>radix astragali</td>
<td>anti-oxidant</td>
<td>Roots of Astragalus membranaceus</td>
<td>3</td>
</tr>
<tr>
<td>vitamin E</td>
<td>anti-oxidant</td>
<td>Vitamin E</td>
<td>3</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>anti-oxidant</td>
<td>Xanthine oxidase inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>astragaloside IV</td>
<td>may modulate immune function</td>
<td>Extract of Astragalus membranaceus</td>
<td>2</td>
</tr>
<tr>
<td>celecoxib</td>
<td>anti-inflammatory</td>
<td>Nonsteroidal antiinflammatory</td>
<td>2</td>
</tr>
<tr>
<td>CoQ10</td>
<td>anti-oxidant</td>
<td>Metabolic coenzyme</td>
<td>2</td>
</tr>
<tr>
<td>dextran-40</td>
<td>increased cochlear blood flow</td>
<td>Colloid; Plasma volume expander</td>
<td>2</td>
</tr>
<tr>
<td>diclofenac sodium</td>
<td>anti-inflammatory</td>
<td>Nonsteroidal antiinflammatory</td>
<td>2</td>
</tr>
<tr>
<td>D-JNKI-1</td>
<td>anti-apoptotic</td>
<td>d-JNK-1 peptide</td>
<td>2</td>
</tr>
<tr>
<td>D-JNKI-1</td>
<td>anti-apoptotic; anti-inflammatory</td>
<td>JNK inhibitor</td>
<td>2</td>
</tr>
<tr>
<td>DSP</td>
<td>anti-inflammatory</td>
<td>Corticosteroid</td>
<td>2</td>
</tr>
<tr>
<td>ethosuximide</td>
<td>anti-excitatory</td>
<td>Anticonvulsant</td>
<td>2</td>
</tr>
<tr>
<td>histamine H1-receptor antagonist</td>
<td>anti-inflammatory</td>
<td>Antihistamine</td>
<td>2</td>
</tr>
<tr>
<td>HPN-07</td>
<td>anti-oxidant</td>
<td>Spin trapping agent</td>
<td>2</td>
</tr>
<tr>
<td>kynurenate</td>
<td>anti-excitatory</td>
<td>Glutamate receptor antagonist</td>
<td>2</td>
</tr>
<tr>
<td>leupeptin</td>
<td>anti-apoptotic</td>
<td>Calpain inhibitor</td>
<td>2</td>
</tr>
<tr>
<td>melatonin</td>
<td>anti-oxidant</td>
<td>Hormone</td>
<td>2</td>
</tr>
<tr>
<td>naftidrofuryl</td>
<td>increased cochlear blood flow</td>
<td>Vasodilator</td>
<td>2</td>
</tr>
<tr>
<td>OTO-104</td>
<td>anti-inflammatory</td>
<td>Corticosteroid</td>
<td>2</td>
</tr>
<tr>
<td>oxygen</td>
<td>increased cochlear oxygen</td>
<td>Oxygen</td>
<td>2</td>
</tr>
<tr>
<td>piracetam</td>
<td>may increase cochlear blood flow</td>
<td>Positive allosteric modulator of the AMPA receptor</td>
<td>2</td>
</tr>
<tr>
<td>PPADS</td>
<td>anti-excitatory</td>
<td>ATP P2X receptor antagonist</td>
<td>2</td>
</tr>
<tr>
<td>resveratrol</td>
<td>anti-oxidant</td>
<td>Polyphenols</td>
<td>2</td>
</tr>
<tr>
<td>R-PIA</td>
<td>anti-oxidant</td>
<td>Adenosine A3 receptor agonist (activates antioxidant enzymes)</td>
<td>2</td>
</tr>
<tr>
<td>Drug/Peptide</td>
<td>Effect</td>
<td>Description</td>
<td>Dosage</td>
</tr>
<tr>
<td>-------------</td>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>R-PIA</td>
<td>anti-excitatory</td>
<td>Adenosine agonist</td>
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<td>vitamins A,C,E and Mg</td>
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<tr>
<td>z-VAD-FMK</td>
<td>anti-apoptotic</td>
<td>Caspase inhibitor</td>
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<td>Pan caspase inhibitor</td>
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<td>(+)-a-tocopherol</td>
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<td>3AB</td>
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<td>APC</td>
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<td>B12</td>
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<td>Compound</td>
<td>Activity</td>
<td>Description</td>
<td>Notes</td>
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<td>anti-excitatory; anti-inflammatory</td>
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<td>Neurotrophin</td>
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<td>CAE</td>
<td>thought to promote DNA repair</td>
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<td>carbamathione</td>
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<td>Partial non-competitive NMDA receptor inhibitor</td>
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<td>anti-oxidant</td>
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<td>NRF2 inducer</td>
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<td>Vasodilator</td>
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<td>cocktail (topiramate, sumatriptin, ibuprofen)</td>
<td>anti-excitatory; anti-inflammatory (note that sumatriptan is a vasoconstrictor and may be ototoxic)</td>
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<td>Compound A</td>
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<td>Compound Vitamin B</td>
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<td>CoQter</td>
<td>anti-oxidant</td>
<td>Metabolic coenzyme</td>
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<td>Extract of Curculigio orchoides</td>
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<td>anti-oxidant</td>
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Table 13 (continued)

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<th>Function/Effect</th>
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<tr>
<td>dextran</td>
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<td>Colloid; Plasma volume expander</td>
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<td>dextran-1</td>
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<td>Colloid; Plasma volume expander</td>
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<td>DFO</td>
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<td>Iron chelator</td>
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<tr>
<td>DHF</td>
<td>Anti-apoptotic; regeneration</td>
<td>TrkB receptor agonist; flavone</td>
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<td>Diazepam</td>
<td>Anti-excitatory</td>
<td>Anticonvulsant</td>
</tr>
<tr>
<td>DFO</td>
<td>Anti-oxidant</td>
<td>Iron chelator</td>
</tr>
<tr>
<td>DHF</td>
<td>Anti-apoptotic; regeneration</td>
<td>TrkB receptor agonist; flavone</td>
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<td>Diazepam</td>
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<td>Anticonvulsant</td>
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<td>DNQX</td>
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<td>Estrogen receptor beta agonist</td>
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<td>hydroxyphenyl)-</td>
<td>anti-apoptotic</td>
<td>Estrogen receptor beta agonist</td>
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<td>propionitrile)</td>
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<td>DSP (dexamethasone</td>
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<td>Corticosteroid</td>
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<td>sodium phosphate)</td>
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<td>DSP Solution</td>
<td>Anti-inflammatory</td>
<td>Corticosteroid</td>
</tr>
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<td>DNA synthesis monitoring probe</td>
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<td>Growth factor</td>
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<td>etanercept</td>
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<td>Regeneration</td>
<td>Growth factor</td>
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<td>GEE</td>
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<td>Amino acid derivative</td>
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<td>Gingko biloba</td>
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<tr>
<td>ginsenoside Rh1</td>
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<td>GSHE</td>
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<td>H2 - molecular</td>
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<td>H2 - molecular hydrogen</td>
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<td>HBOT</td>
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<td>Hyperbaric oxygen</td>
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100
Table 13 (continued)

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<td>hydrogen-saturated saline</td>
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<td>gas</td>
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<td>IBO</td>
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<td>Isobaric oxygen</td>
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<td>ifenprodil</td>
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<td>Selective STAT3/JAK2 inhibitor</td>
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<td>Compound</td>
<td>Effect</td>
<td>Category</td>
<td>Notes</td>
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<td>Methylene blue</td>
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<td>Cyanide antidote</td>
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<td>Methylene blue (3,7-bis(dimethylamino) phenazathionium chloride; MB)</td>
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<td>Cyanide antidote</td>
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<td>Metal chelator, nitric oxide synthase inhibitor, NF-kB inhibitor</td>
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<td>pifithrin alpha (PFT)</td>
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<td>Anesthetic</td>
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</tr>
<tr>
<td>RU28318</td>
<td>n/a; used for hypothesis testing</td>
<td>Mineralocorticoid receptor antagonist</td>
<td></td>
</tr>
<tr>
<td>RU38486</td>
<td>n/a (used for testing, not as therapy)</td>
<td>Glucocorticoid receptor (GR) antagonist</td>
<td></td>
</tr>
<tr>
<td>RU487</td>
<td>ion homeostasis</td>
<td>Glucocorticoid receptor antagonist</td>
<td></td>
</tr>
<tr>
<td>RU488</td>
<td>ion homeostasis</td>
<td>Glucocorticoid receptor antagonist</td>
<td></td>
</tr>
<tr>
<td>SB extract</td>
<td>anti-excitatory; anti-inflammatory</td>
<td>Extract of Scutellaria baicalensis</td>
<td></td>
</tr>
<tr>
<td>SB202190</td>
<td>Anti-apoptotic; regeneration</td>
<td>p38 MAPK inhibitor</td>
<td></td>
</tr>
<tr>
<td>SB202474</td>
<td>Anti-apoptotic; regeneration</td>
<td>p38 MAPK inhibitor</td>
<td></td>
</tr>
<tr>
<td>SB203580</td>
<td>Anti-apoptotic; regeneration</td>
<td>p38 MAPK inhibitor</td>
<td>1</td>
</tr>
<tr>
<td>SC58125</td>
<td>anti-inflammatory</td>
<td>Nonsteroidal antiinflammatory</td>
<td>1</td>
</tr>
<tr>
<td>siAMPKα1</td>
<td>anti-apoptotic</td>
<td>siRNA against AMPK</td>
<td>1</td>
</tr>
<tr>
<td>siLKB1</td>
<td>anti-apoptotic</td>
<td>siRNA against LKB1</td>
<td>1</td>
</tr>
<tr>
<td>silymarin</td>
<td>anti-oxidant</td>
<td>Extract of milk thistle; flavenoid complex</td>
<td>1</td>
</tr>
<tr>
<td>siRadixin</td>
<td>n/a; used for hypothesis testing</td>
<td>siRNA</td>
<td>1</td>
</tr>
<tr>
<td>siRIP3</td>
<td>anti-apoptotic</td>
<td>siRNA against RIP3</td>
<td>1</td>
</tr>
<tr>
<td>siROCK2</td>
<td>n/a; used for hypothesis testing</td>
<td>siRNA - ROCK2 (cytoskeletal integrity)</td>
<td>1</td>
</tr>
<tr>
<td>sodium enoxaparin</td>
<td>increased cochlear blood flow</td>
<td>Anticoagulant</td>
<td>1</td>
</tr>
<tr>
<td>sodium thiosulfate (STS)</td>
<td>anti-oxidant</td>
<td>Cyanide antidote</td>
<td>1</td>
</tr>
<tr>
<td>SOD-PEG</td>
<td>anti-oxidant</td>
<td>Metabolic enzyme (bovine-derived)</td>
<td>1</td>
</tr>
<tr>
<td>spironolactone</td>
<td>n/a; used for hypothesis testing</td>
<td>Mineralocorticoid receptor antagonist</td>
<td>1</td>
</tr>
<tr>
<td>Stealth-nano–BP</td>
<td>anti-inflammatory</td>
<td>Corticosteroid</td>
<td>1</td>
</tr>
<tr>
<td>Stealth-nano–rhodamine</td>
<td>n/a; used for hypothesis testing</td>
<td>Assay marker</td>
<td>1</td>
</tr>
<tr>
<td>T-817MA</td>
<td>anti-apoptotic, anti-oxidant</td>
<td>Sigma-1 receptor agonist</td>
<td>1</td>
</tr>
<tr>
<td>tacrolimus</td>
<td>anti-apoptotic; anti-inflammatory</td>
<td>Immunosuppressant</td>
<td>1</td>
</tr>
<tr>
<td>thymoquinone</td>
<td>anti-oxidant; anti-inflammatory</td>
<td>Extract of Nigella sativa</td>
<td>1</td>
</tr>
<tr>
<td>trimethadione</td>
<td>anti-excitatory</td>
<td>Anticonvulsant</td>
<td>1</td>
</tr>
<tr>
<td>trolox</td>
<td>anti-oxidant</td>
<td>Vitamin E analog</td>
<td>1</td>
</tr>
<tr>
<td>vitamin B complex (B1, B6 and B12)</td>
<td></td>
<td>Vitamin B Complex</td>
<td>1</td>
</tr>
<tr>
<td>vitamin B1</td>
<td>metabolic coenzyme</td>
<td>Vitamin B1</td>
<td>1</td>
</tr>
<tr>
<td>vitamin B12</td>
<td>cofactor for synthesis of nucleic acids, proteins, hormones, etc</td>
<td>Vitamin B12</td>
<td>1</td>
</tr>
<tr>
<td>vitamin B6</td>
<td>supports neurotransmitter synthesis</td>
<td>Vitamin B6</td>
<td>1</td>
</tr>
<tr>
<td>Substance</td>
<td>Function</td>
<td>Effect</td>
<td>1</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>---</td>
</tr>
<tr>
<td>vitamin E ((±)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid, “Trolox,”)</td>
<td>anti-oxidant</td>
<td>Vitamin E</td>
<td>1</td>
</tr>
<tr>
<td>XIAP</td>
<td>anti-apoptotic</td>
<td>Cell-penetrating peptide of XIAP gene</td>
<td>1</td>
</tr>
<tr>
<td>XIAP-9R (“X-linked inhibitor of apoptosis protein” (XIAP) bonded to a 9R peptide)</td>
<td>anti-apoptotic</td>
<td>Cell-penetrating peptide of XIAP gene</td>
<td>1</td>
</tr>
<tr>
<td>zinc-protoporphyrin-IX</td>
<td>n/a; used for hypothesis testing</td>
<td>Heme oxygenase inhibitor</td>
<td>1</td>
</tr>
<tr>
<td>zonisamide</td>
<td>anti-excitatory</td>
<td>Anticonvulsant</td>
<td>1</td>
</tr>
<tr>
<td>α-lipoic acid</td>
<td>anti-oxidant</td>
<td>Metabolic cofactor</td>
<td>1</td>
</tr>
<tr>
<td>β-histine</td>
<td>increased cochlear blood flow; anti-excitatory</td>
<td>Histamine H1 agonist, H3 antagonist</td>
<td>1</td>
</tr>
<tr>
<td>β-histine-2 HCl</td>
<td>increased cochlear blood flow; anti-excitatory</td>
<td>Histamine H1 agonist, H3 antagonist</td>
<td>1</td>
</tr>
<tr>
<td>β-methasone phosphate (BP)</td>
<td>anti-inflammatory</td>
<td>Corticosteroid</td>
<td>1</td>
</tr>
</tbody>
</table>
Figure 20. Snapshot of most frequently investigated agents for NIHL

Figure 20 provides a snapshot of the drugs studied most often (k $\geq 31$), while Figure 21 suggests potentially interesting trends, albeit possibly too recent to call them true trends, of growing investigations in small molecules and declining research in nutraceutical research, although additional time may be needed to see how these trends continue to develop. It may be the case that poor translation to humans of the latter, combined with growing advocacy and global awareness of NIHL prevalence is spurring interest and focus into repurposing small molecules for this indication.
Further PIHL Group analysis with particular focus and inputs from SMEs in otology are needed to decipher meaningful interpretations of the drug dosing and scheduling, combined also with the administration routes. While all practical applications favor oral tablet with limited dosing schedules, the evidence may show that the highest prospects for success lay in intratympanic, direct access routes which come with higher risk, lower patient acceptability, higher costs, and higher degree of skill and facility requirements to administer. All of these will factor into commercialization and development decisions as well as acquisition decisions from medical payers and patients alike.
3.7 Analytic Plans/Reporting

There was limited quantifiable data collected here. The intent of collecting the descriptive information was to allow the PHIL group members with interest in defining recommended statistical models access to information that could be subjected to word searches and other manual, qualitative assessments of tests in order to determine best test batteries to apply toward common primary endpoints. Given that many primary endpoints will still require consensus on definitions to use – i.e., definition of hearing threshold in DPOAEs or ABRs in animal studies, which, as touched upon in the Measures section, still vary greatly – any statistical analysis plans will be secondary, dependent objectives for PIHL to tackle.

Of interest, 21 articles did not report any analytical plan details and almost no studies provided a description of their sample size determination methods and power analysis. When it was mentioned, it was generally in the context of why an arbitrary number of subjects was selected for exploratory/pilot experiments. This speaks volumes about the state of reporting quality, when a primary aim of both CONSORT and ARRIVE guidelines is to increase potential for reproducibility. How can any outcomes be reproduced when the keystone to how they were derived is missing? What’s more, the scientific integrity of a study depends upon fundamental trust that the experimental process itself was followed, which is questionable when transparent accounts of data manipulation are missing.

Critical assessment of ad hoc analysis and how those results are translated into reported outcomes will also be of interest for further scrutiny.
3.8 Outcomes: Summative Thoughts

Like the Analytic fields, so too the Outcomes fields were only intended to capture descriptive outcomes that may be of most interest to the PIHL group objectives and/or hold potential for any comparisons with other variables quantifiably captured above. There was an option developed to title each outcome statement copied into the database, and those headings allow sorting by:

- primary outcome (often a simple statement of positive or negative outcomes from the abstract or conclusion sections)
- injury – reports of damage (by whatever measures were used) to placebo or control groups
- safety – adverse event reports
- dose response, indication differences (i.e., prophylactic vs rescue paradigms), time points differences (i.e., TTS vs PTS)
- specific outcomes/efficacy statements by measure

Only the first two on this list were provided and thus collected with any consistency, but these do not constitute data capable of meta-analysis. And given the myriad of ways investigators chose to design exposures, measures, drug delivery paradigms, and statistical analysis, there is no magical Rosetta stone to translate and align each element. However, meaningful comparisons can still be made using this dataset, particularly using subsets of matching data. For example, same-type noise exposures may be correlated to TTS in animal studies using ABR measures across a common set of frequencies. Using a
narrowed lens of common elements, some outcomes comparisons may be possible with adequate teams of PIHL group SMEs interpreting the variables.

The capture will hopefully provide the reference material needed to make judgement calls on best approaches for other design elements. Connecting Injury Outcomes to Noise Exposure records, as exemplified above, may offer new insights in to the damage models used, thus paving the way for recommendations based on the damage future investigators wish to produce, thus avoiding undue wasted animals and time that results from investigations which start with preliminary studies to specify the damage paradigm, which was reported in several efforts. Overall, the Outcomes text can be mined as needed for any particular inquiry to the database since many proverbial pearls of interest were recorded there – measures which appeared to be most sensitive to change, exposures which resulted in too little damage to show intervention results, ideal time points to examine the permanent damage state, etc.

Outcomes reports can also speak to bias in reporting. Selective data analysis plan reporting confound the issue when scant outcomes are provided yet positive results are touted in the abstract and conclusion sections of these articles by and large. With an average of 3.87 separate outcome statements recorded per article, selecting one overall positive, negative or neutral outcome representative of the primary aim of each study

2 This is an anecdotal recollection from data extraction efforts, and is not recorded as a variable in this dataset.

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resulted in 85% positively reported articles. However, many positive reports were the result of highly selective results and/or post hoc analysis (i.e., at one among three tested doses or only in higher frequencies tested, etc.). Even reported negative outcomes were often downplayed with additional outcome comments about more positive post hoc analysis performed. While these are important observations to note, they generally are not considered prime material to include in an abstract meant to convey overall study outcomes, yet they often were. Considering the lack of translation to approved products for human use, it seems safe to assume these factors may be strong indicators of reporting bias in PIHL research, but whether it is publication bias (selective acceptance for publication on the part of the journals) or outcome reporting bias (selective submissions from the investigators) remains to be determined. The PIHL group strategy is poised to address them both.
Chapter 4: Results - Primary Aim 2

4.1 PIHL ACCOMPLISHMENTS AND BEST PRACTICE RECOMMENDATIONS

4.1.1 Formation: Overcoming competing agendas

The development of the PIHL group has been an undeniable success. With very little dedicated resourcing, dozens of participants come together every month, every quarter and every other year to meet, discuss and tackle the objectives jointly developed. The idea of serving a superordinate, patriotic mission to contribute to solutions for our nation’s heroes has surely played a part, but recognizing and playing to the diverse interests brought from each stakeholder group is surely behind the lasting participation seen. As developed in the 1960’s by Victor Vroom, the Expectancy Theory captures the PIHL group dynamic: the group presents a gentle threat that declining participation in the group at even an observational level could leave one at a disadvantage for funding or partnership opportunities, awareness of latest news or developments, or a seat at the table in determining guidance which they will eventually be asked to follow (Vroom, 1964). In exchange for their continuing, consistently good service (effort/performance), participants are rewarded with the benefit of being “in the know”, part of the solution, with a front row view of any news or information that could potentially benefit their pursuits, and the results have shown a steady increase in membership every year since its inception.

The PIHL group has never attempted to hide or shy away from the competing agendas present at the table; rather, it has always addressed them up front. As seen
Appendices B.2 and B.5, the introductory talks to the PIHL biennial meetings, the proverbial elephant in the room was literally called out and discussed. Conflict of Interest Disclosure forms are collected and maintained from all members, particularly for evaluation upon contribution to published guidance products to ensure transparency is maintained yet inclusion is not hindered but grows.

The core of participation began with investigators of PIHL research. These SMEs are the drivers of standards and will be the first adopters of best practices. They are highly incentivized to utilize evidence-based research practices because, just as EBP maximizes clinical efficiencies, BRPs – above and beyond proof of adherence to Good Laboratory Practices (GLPs) and Good Clinical Practices (GCPs) already expected – stand to maximize research efficiencies. Submission of a protocol to an IRB and IND package to the FDA which adheres to known and accepted BRPs ought to streamline review concerns and expedite regulatory approval processes. Similarly, funding proposals which include BRP methodology ought to ease concern of risk for portfolio managers and award review boards, thus increasing chances for funding awards. Finally, following BRPs should eliminate peer review concerns regarding potentially questionable study design during publication processes. This should grow the footprint for PIHL research in prestigious journals and/or conference podium slots, thus in turn strengthening the evidence base further.
The growth to stakeholders beyond the investigator core is of pivotal importance to this model depicted in Figure 23 (and presented at ARO’s 2017 Mid-Winter Meeting and NHCA’s 2017 Annual Meeting, see Appendices E7 and E8) (Hammill, 2017a & 2017b). Participation of the regulatory bodies, funding agencies, and journal and conference boards provides them with direct access to State-of-the-Science and BRPs in PIHL research for their use in policy and decision-making. Further, their inclusion permits their contributions to ongoing dialogue about issues or concerns regarding adoption and
implementation of BRPs for the approval pathways in their purview. Meanwhile, the PIHL Group at large maintains the platform for community engagement, cross-talk, consensus, and buy-in for rapid adoption across the spectrum of participants.

4.1.2 Newsletters and low-hanging fruit

“The increasing volume of research activities, from basic research through clinical trials, currently underway to understand the mechanisms behind hearing loss as well as potential pharmaceutical interventions that may reduce this health issue is both incredibly exciting and often difficult to keep up with.”

This statement in the editorial to the 3rd PIHL newsletter summarizes the intent of the newsletters overall (Hammill & Packer, 2015). While the first two editions were focused on concepts born from the Animal Committee, the third edition and all editions thereafter grew the Newsletter concept and utility to encompass the entire PIHL community scope.

Features common to each issue include a literature search of PIHL relevant publications since the last newsletter release, guest editor-selected research highlight discussions, current clinical trials listed on ClinicalTrials.gov, and “white paper”-style guidance documents developed by the group. These white papers circulate the concepts and determinations that will be developed into peer-reviewed publications, thus providing opportunity for dissent, discussion and revisions prior to the final step in BRP development.
– namely, peer-reviewed publication. These newsletters create a manageable platform for dissemination and understanding of the overall current state of the PIHL sciences. They are disseminated as open access postings on the HCE’s website (https://hearing.health.mil/Research/PIHL-Working-Group/PIHL-Newsletters).

Volunteers are solicited among rotating committees within PIHL group to serve as guest editors. The first two newsletter editors focused on basic science and animal model issues, while the editors for Edition three tackled the clinical focus. The clinical guidance white papers written for the latter were also develop into a major workshop at the Association for Research in Otolaryngology Conference (see 4.3 below) as well as published in full manuscript form in the special issue of Otology & Neurotology discussed in sections 4.4 and 5.2 below. The fourth newsletter was conceived by the Sound Committee, and the guest editors had the novel addition of seminal articles in acoustic science and noise controls for reference materials to investigators who may not be as familiar with these fields as they are with molecular intervention pathways. Edition five was again “assigned” to the Animal Committee, and the guest editors focused on new developments in Hidden Hearing Loss. Guidance from editions four and five was expanded in the resulting Hearing Research special issue. These two committees collaborated to develop and pitch the issue to the journal, shared guest editorial roles, and completed the issue together. There are six newsletters in total, the latest edition completed in the Fall of 2016 with a focus in ototoxicity. This, too, was a precursor to the special issues developed for both the International Journal of Audiology and Frontiers of Cellular Neuroscience.
The seventh newsletter is planned for release in the Fall of 2017 and will have a focus on the outcomes of the systematic review described in this thesis with the goal of stimulating deeper analytic efforts using this data. As with previous newsletters, this will serve as a stepping stone to yet another special issue of articles focused on BRPs and targeted conference dissemination. But the most critical dissemination pathway is right back through the extensive PIHL network (see Figure 24 and Appendix E.7). This pathway depicts the identification, prioritization, and topic development that occurs within the PIHL group (Step 1); the development of white papers for dissemination and refinement stages of BRPs (Step 2); the dissemination of BRPs through both conference and journal pathways which target maximum reach and interest particularly through broad scope efforts such as workshops and special issues (Steps 3 & 4); and the dissemination to and adoption back through the ever-expanding PIHL network, including the funding, regulatory, and publication gatekeepers to the field. The final step in this cycle is, in reality occurring continuously the process through various communication platforms utilized by the group. Such repetitive reinforcement of knowledge dissemination is more likely to result in adoption among even the most knowledge-saturated and least engaged PIHL members.
4.2 CONFERENCE PROCEEDINGS

Much of the success of the PIHL group has come from marketing and social interactions during times of conference. First targeting opportunities to “preach to the choir” – those professionals with direct concern and engagement with PIHL research – the PIHL group and its messaging has been delivered at the National Hearing Conservation Association (NHCA), Association for Research in Otolaryngology (ARO), American Academy of Audiology (AAA), the Military Health Service Research Symposium (MHSRS), and Joint Defense Veterans Audiology Conference (JDVAC) annual conferences (see Appendices E.1 – E.9 for presentations and posters delivered). Each
conference targets a unique (albeit overlapping) audience among relevant domains of stakeholders. Table 14 outlines these targets in more detail.

Table 14. Conference presentation targets for PIHL dissemination and stakeholder engagement pathway.

<table>
<thead>
<tr>
<th>Association/Conference</th>
<th>Attendee Estimates</th>
<th>Primary Audience</th>
<th>Content to Disseminate</th>
<th>PIHL Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Hearing Conservation Association (NHCA) / Annual Meeting</td>
<td>&gt; 300</td>
<td>Hearing Conservation (Audiologists, Industrial Hygienists, Epidemiologists, Occupational Health specialists, Acoustic Scientists)</td>
<td>PIHL Group Mission and Outcomes; BRPs for field trials research and acoustic elements of basic and clinical research</td>
<td>Podium 2016; 2017</td>
</tr>
<tr>
<td>Association for Research in Otolaryngology (ARO) / Mid-Winter Meeting</td>
<td>&gt; 1,800</td>
<td>Bench-to-Bedside Investigators in Audiology and Vestibular Research</td>
<td>PIHL Group Mission and Outcomes; BRPs in preclinical and clinical research</td>
<td>Workshop (8 Podiums) 2016; Poster 2017; Target for Symposium 2018 (Mechanisms of Ototoxicity) &amp; 2019 (BRPs based on the systematic review)</td>
</tr>
<tr>
<td>Event</td>
<td>Attendance</td>
<td>Audience</td>
<td>Focus Areas</td>
<td>Target Year</td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>----------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>American Academy of Audiology (AAA) / AudiologyNOW!</td>
<td>&gt; 7,000</td>
<td>Clinical Audiologists</td>
<td>Clinical Trial updates, State-of-the-Science; Clinical Trial BRPs</td>
<td>Podium 2013; Targeted for 2019</td>
</tr>
<tr>
<td>Military Health Service Research Symposium (MHSRS) / Annual Meeting</td>
<td>&gt; 2,000</td>
<td>International Military Medical/ Health Research Stakeholders</td>
<td>PIHL Group Mission and Outcomes</td>
<td>Podium 2013; Poster 2015</td>
</tr>
<tr>
<td>Joint Defense Veterans Audiology Conference (JDVAC) / Annual Meeting</td>
<td>&gt; 300</td>
<td>Clinical and Occupational U.S. Military and VA Audiologists</td>
<td>Clinical Trial updates, State-of-the-Science</td>
<td>Podium 2014; Targeted for 2018</td>
</tr>
<tr>
<td>Academy of Otolaryngology - Head Neck Surgery</td>
<td>&gt; 5,000</td>
<td>International ENT Physicians, Clinical Audiologists</td>
<td>Clinical Trial BRPs</td>
<td>Targeted for 2018</td>
</tr>
<tr>
<td>American Speech-Language-Hearing Association (ASHA) / Annual Convention</td>
<td>&gt; 15,000</td>
<td>Clinical Audiologists and Speech-Language Pathologists</td>
<td>Clinical Trial BRPs</td>
<td>Targeted for 2018</td>
</tr>
<tr>
<td>World Congress of Audiology</td>
<td>&gt; 1,000</td>
<td>International Clinical Audiologists</td>
<td>Clinical Trial BRPs</td>
<td>Targeted for 2018</td>
</tr>
</tbody>
</table>
In addition to the presentations themselves, efforts have been made to hold an annual social event at the ARO conference where the largest number of PIHL members attend one event. This event – intentionally informal, non-sponsored, and social – provides the opportunity to put faces with names and allow in-person conversation, an invaluable contribution in the pursuit of any virtually-based organization. It has drawn dozens of participants over the four years it has been held, resulting in fruitful conversations, new or strengthened friendships, and ultimately, new collaborative relationships.

4.3 Journal Editions

After BRPs have gone through the processes described above, they are ready for publication in well-known peer-reviewed journals as a final dissemination effort. Just as each conference targets a unique group of stakeholders, so too, the journal publication pathway has been developed to both reach the intended audiences and forge relationships with the journals themselves. The former aim grows credibility for the PIHL Group and the latter gains entrance points for conversation about future efforts for furthering the BRP adoption process through the publication peer-review and revision process. Each of the journals targeted are compiled in the summary Table 15, following the short descriptions provided in 4.4.1 – 4.4.4 below. Articles on which I served as a co-author are included as chapters in this thesis as noted in italicized comments below.
4.3.1 Otology & Neurotology: PIHL Research Guidance Papers

The first completed special issue was released in September of 2016 in Otology & Neurotology. This issue contained 8 articles, including the editorial introduction. Although the PIHL papers did not comprise the entire issue, it did receive a byline on the cover (see figure 25). The articles included:

**Guest Editorial – Issue Introduction** Hammill & Packer 2016, *see Chapter 5.2.1*

- Guidelines for Auditory Threshold Measurement for Significant Threshold Shift (STS) (Campbell et al., 2016, *see Chapter 5.2.2*)
- Biomarkers of Oxidative Damage and Inflammation: Experiences in Hearing and Balance Disorders (Haase, 2016)
- The Genomic Basis of Noise-Induced Hearing Loss: A Literature Review Organized by Cellular Pathway Categories (Clifford et al., 2016)
- Serial Monitoring of Otoacoustic Emissions in Clinical Trials (Konrad-Martin et al., 2016)
- Speech-in-noise tests and supra-threshold auditory evoked potentials as metrics for noise damage and clinical trial outcome measures (Le Prell & Brungart, 2016)
- Measurement of Tinnitus (Henry, 2016)
- Temporary and Permanent Noise-Induced Threshold Shifts (Ryan et al., 2016, *see Chapter 5.2.3*)
4.3.2 Hearing Research: Noise and the Military

The second special issue was modeled after an earlier issue published by Hearing Research in 2007 (Volume 226; Issues 1-2, April 2007). The first issue was the result of a DoD-sponsored meeting that took place in 2005, which included a variety of stakeholders invited to discuss PIHL research and the state-of-the-science. The 2005 issue is jointly focused on mechanisms of NIHL and Ototoxicity. In the PIHL group’s effort to update the field, two joined topic areas were again developed, this time focusing instead on noise, with a collection of articles discussing noise injury within the military environment (section 1), and mechanisms of action of NIHL (section 2). Unique cover art was selected by co-editors from the HCE (Col (retired) Mark Packer and Tanisha Hammill), the Office of Naval Research (Kurt Yankaskas), and Academia (St. Jude’s Jian Zuo). The 23 articles are all available online and are scheduled for July 2017 print release.

Guest Editorial: Yankaskas, Packer, Hammill & Zuo (Yankaskas et al., in review, see Chapter 5.3.1)

**Issue 1: Impact of noise in the military**

- Prevalence of hearing loss and tinnitus in Iraq and Afghanistan veterans: A Chronic Effects of Neurotrauma Consortium Study (Swan et al., 2017)
- Hearing testing in the U.S. Department of Defense: Potential impact on Veterans Affairs hearing loss disability awards (Nelson et al., 2016)
- Audiologic Characteristics in a Sample of Recently-Separated Military Veterans: The Noise Outcomes in Servicemembers Epidemiology Study (NOISE Study) (Gordon et al., 2016)
- Long-Term Noise Exposures: A Brief Review (Davis, 2016a)
- Impulsive Noise: A Brief Review (Davis, 2016b)
- Engineering out the Noise (Yankaskas et al., 2017)
• Noise Dosimetry for Tactical Environments (Smalt et al., 2016)
• Performance in Noise: Impact of Reduced Speech Intelligibility on Sailor Performance in a Navy Command Environment (Keller et al., 2016)
• The Effect of Sensorineural Hearing Loss and Tinnitus on Speech Recognition over Air and Bone Conduction Military Communications Headsets (Manning et al., 2016)
• Effects of Noise on Speech Recognition: Challenges for Communication by Service Members (Le Prell et al., 2016)
• Development and Validation of the Speech Reception in Noise (SPRINT) Test (Brungart et al., 2017)
• Sensory coding and cognitive processing of sound in Veterans with blast exposure (Bressler et al., 2016)

**Issue 2: Biological mechanisms**
• Analytical and Numerical Modeling of the Hearing System: Advances Towards the Assessment of Hearing Damage (Paolis et al., 2017)
• Cellular Mechanisms of Noise-Induced Hearing Loss (Kurabi et al., 2016)
• Cochlear Synaptopathy in Acquired Sensorineural Hearing Loss: Manifestations and Mechanisms (Liberman et al., 2017)
• Noise-Induced Cochlear Synaptopathy: Past Findings and Future Studies (Kobel, et al., 2016)
• Evidence of “hidden hearing loss” following noise exposures that produce robust TTS and ABR wave-I amplitude reductions (Lobarinas et al., 2016)
• Translational issues in cochlear synaptopathy (Hickox et al., 2017)
• A Review of the Progress and Pitfalls of FDA Policy Process: Planning a Pathway for Pharmaceutical Interventions for Hearing Loss Development (Hammill, 2016, *see Chapter 5.3.2*)
• Drug discovery for hearing loss: Phenotypic screening of chemical compounds on primary cultures of the spiral ganglion (Whitlon et al., 2016)
• Cochlear hair cell regeneration after noise-induced hearing loss: does regeneration follow development? (Zheng, et al., 2016)
• Auditory Thalamic Circuits and GABA receptors: Putative Mechanisms in Tinnitus Pathology (Caspary et al., 2016)
• Tinnitus and Hyperacusis: Contributions of Paraflocculus, Reticular Formation and Stress (Chen et al., 2017)

4.3.3 International Journal of Audiology: Ototoxicity Clinical Monitoring

When the PIHL group turned interest and focus on the topics inherent to Ototoxicity in the Spring of 2016, two distinct special issues were mapped out: the first would cover clinical monitoring issues and the second would be a thorough review of mechanisms of ototoxic hearing loss. The latter is described in 4.4.4 below. The first issue includes eleven articles in draft or peer-review/publication stages. These articles are intended to orient the audiologist (primary readership of the International Journal of Audiology) to issues concerning standardization of monitoring protocols, understanding sources of ototoxicity in both clinical and occupational settings, and setting future directions for research in measure development and PIHL studies. The articles being developed for publication include (authors list still pending):

• Introduction to Pharmacologic Agents of Ototoxicity
• Introduction to Non-Pharmacologic Agents of Ototoxicity (Hammill et al., in review as of the publication date of this thesis; see Chapter 5.4.1)
• Ototoxicity Scales for Clinical Trials: Benefits/Limitations
• Ototoxicity Monitoring for Adult Patients
• Ototoxicity monitoring in children treated with platinum chemotherapy
• Monitoring neonates for ototoxicity
• Vestibulotoxicity: Strategies for clinical diagnosis and rehabilitation
• Cisplatin ototoxicity remains a major concern for head and neck cancer patients
• Ototoxicity monitoring through the eyes of the treating physician: Perspectives from pulmonology, infectious diseases, and medical oncology
• Ototoxicity Monitoring: Tablet-based testing
• Protection for medication-induced hearing loss: The state of the Science (Hammill & Campbell., in review as of the publication date of this thesis; see Chapter 5.4.2)

4.3.4 Frontiers of Neuroscience, Cellular Topics

The next issue under development has been arranged to be published in the high-impact factor journal, Frontiers of Neuroscience, in a Cellular Topics special issue. One of the PIHL committee leaders in Ototoxicity, Peter Steyger, is the lead guest editor for this issue. There is an ongoing evaluation of the 23 abstracts submitted for potential inclusion. This upcoming issue provides the updates to the ototoxicity section of the 2005 Hearing Research issue discussed above.
Table 15. Journal publication targets for PIHL dissemination and stakeholder engagement pathway.

<table>
<thead>
<tr>
<th>Journal/Publication</th>
<th>Impact Factor</th>
<th>Typical Readership</th>
<th>Content to Disseminate</th>
<th>PIHL Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otology &amp; Neurotology</td>
<td>1.953</td>
<td>Ear, Nose &amp; Throat (ENT) Physicians</td>
<td>BPRs in clinical trials</td>
<td>Published, open access</td>
</tr>
<tr>
<td>Hearing Research</td>
<td>3.565</td>
<td>Basic Scientists</td>
<td>State-of-the-science and BPRs for basic science, mechanisms of action with translational focus</td>
<td>In press</td>
</tr>
<tr>
<td>International Journal of Audiology</td>
<td>1.681</td>
<td>Clinical and Occupational Audiologists</td>
<td>State-of-the-science and BPRs for clinical practice and clinical trials in ototoxicity</td>
<td>Submissions in review</td>
</tr>
<tr>
<td>Frontiers of Neuroscience</td>
<td>3.398</td>
<td>Basic Scientists</td>
<td>State-of-the-science and BPRs for basic research in ototoxicity</td>
<td>Approved special issue in development</td>
</tr>
<tr>
<td>Public Health</td>
<td>1.566</td>
<td>Public Health Professionals</td>
<td>State-of-the-science and BPRs for surveillance and data collection</td>
<td>Future target</td>
</tr>
<tr>
<td>PloS One</td>
<td>4.411</td>
<td>Broad readership</td>
<td>Dissemination of the PIHL model</td>
<td>Future target</td>
</tr>
<tr>
<td>Audiology &amp; Neuro-Otology</td>
<td>1.776</td>
<td>Audiologists and ENT</td>
<td>Dissemination of clinical trial BPRs resulting from this systematic review evidence base.</td>
<td>Future target</td>
</tr>
<tr>
<td>Noise &amp; Health</td>
<td>0.739</td>
<td>Industrial Hygenists; Audiologists</td>
<td>Dissemination of BPRs related to noise exposures resulting from this systematic review evidence base.</td>
<td>Future target</td>
</tr>
</tbody>
</table>
4.3.5 Next targets

Where journal publications and conference proceedings have thus far been targeting broad engagement with primary stakeholders to date, future efforts will begin to broaden the reach to other affiliated stakeholders. Examples include targeting Public Health journal and American Public Health Association (APHA) audiences with updates on PIHL progress and recommendations for comprehensive monitoring to prepare for comparable post-market studies that measure clinical effectiveness and population-wide impacts of new therapies. Additionally, once results of the systematic review are more thoroughly developed by the PIHL SMEs, larger impact journals like *PloS One* will be targeted for broad dissemination of the overall strategic model for translational science management proposed herein.
Chapter 5: Manuscripts

Chapter Overview

The manuscripts written as part of this effort were designed to contribute to either the foundational understanding required to design this project or one of the primary aims discussed above through delivery of the first BRPs to come out of the PIHL group, or the state-of-the-science foundations upon which future, evidence-based BRPs will be built. The following manuscripts\(^3\) have been published in peer-reviewed journals or are currently

\(^3\) The manuscripts included below, and the contributions of this author to coauthored manuscripts, include:


*As co-author, I performed literature review, co-wrote, and contributed revisions to the manuscript.*


*As sole author, I performed literature review, wrote and edited the manuscript, submitted the article for publication, and completed all requested revisions.*


*As co-author, I performed literature review, co-wrote and edited the manuscript, and submitted the article for publication. Revisions are pending.*
undergoing peer review. All manuscripts are included with express, written permissions from the publishing organizations.


*As co-author, I performed literature review, co-wrote and edited the manuscript, and submitted the article for publication. Revisions are pending.*


*As co-author, I performed literature review, co-wrote and edited the manuscript, submitted the article for publication, and completed all revisions required. Further, I served as the primary coordinator of the special issue for 7 articles total.*


*As co-author, I performed literature review, co-wrote, and contributed revisions to the manuscript.*


*As co-author, I performed literature review, co-wrote and edited the manuscript, and submitted the article for publication. Further, I served as one of three coordinators of the special issue for 22 articles total.*
5.1 EPIDEMIOLOGY

Separate, but related, efforts have been described in three manuscripts that were not formally part of this dissertation project and thus these are referenced rather than included. Cooper et al. (2014), Alamgir et al. (2014), and Alamgir et al. (2016) describe the development of and models used in an ongoing effort led by the HCE to characterize the incidence and prevalence of noise-induced hearing injury among U.S. military Service members as well as to determine the economic burden those injuries impose upon the DoD. Prior to this effort, data were collected from various agencies within the DoD on select groups of Service members and associated costs, but no comprehensive collection of data not assessment had ever been undertaken. These manuscripts describe the formation of these very complex epidemiological pursuits which were designed to answer key PIHL objectives concerned with 1) the DoD markets for PIHL technologies required for commercialization package development, and 2) identification of viable Service member populations in which PIHL clinical trials could be conducted. Preliminary results of these efforts have not yet been published but the contract report is expected to publish open access in the Defense Technical Information Center (dtic.mil) the end 2017.
5.2 **Otology & Neurotology Special Issue: Clinical Guidance**

The first set of best research practices developed by the PIHL group model (conducted prior to this systematic review) were selected via PIHL consensus and were published in Otology & Neurotology in September 2016 with open access made possible by HCE sponsorship. The manuscripts included herein only include those co-authored, including 5.2.1) the editorial to the collection which describes the overarching goal of providing best research practices for PIHL, as detailed in this dissertation (Hammill & Packer, 2016); 5.2.2) a BPR guidance paper for capturing auditory thresholds in clinical trials (Campbell et al, 2016); and 5.2.3) a BPR guidance paper to determine and define the difference between temporary threshold shifts and permanent threshold shifts (Ryan et al., 2016). Efforts included conceiving and organizing the special issue with the journal editor, in collaboration with Col (retired) Mark Packer, as well as researching, writing, and editing sections of the manuscripts included herein.
Both Military and Civilian noise threats continue to claim casualties. Degradation of quality of life and limitations in communication, opportunities and performance can be expected to continue to escalate, marginalizing significant portions of the nation. Every year, hearing injuries top the lists of Veterans Affairs (VA) disability tables. Over 2.3 million Veterans claimed an auditory injury in fiscal year 2014 alone (2014 Annual Veteran Benefits Report). While noise control engineering, administrative noise exposure controls and hearing protection education and devices are all important tools in the military arsenal against noise injury, a pharmaceutical tool to augment prevention or mitigate injury is needed.

The increasing volume of research activities, from basic research through clinical trials, currently underway to understand the mechanisms behind hearing loss as well as
potential pharmaceutical interventions that may reduce this health issue is both incredibly exciting and often difficult to keep up with. The Pharmaceutical Interventions for Hearing Loss (PIHL) working group was chartered in 2012 by the Department of Defense (DoD) Hearing Center of Excellence (HCE) to review and maintain state of the science knowledge of these translational therapies for the prevention and rescue of noise- and ototoxic-induced hearing loss. The group is comprised of nearly 175 members, voluntarily participating from DoD, VA, Centers for Disease Control (CDC) National Institute for Occupational Safety and Health (NIOSH), Food and Drug Administration (FDA), Academia, Industry (both biotechnology and venture capital firms), as well as international partners and stakeholders.

To date, PIHL scientists have no defined standards to guide study design. Instead, they must rely on cursory reviews of existing articles, mentored practices, or their own best judgment. The lack of homogeneous study designs result in incomparable, and thus disputable, study outcomes which, in turn, delays in our ability to understand and progress the state of the science. The PIHL group’s charter calls upon the members to determine and maintain the current and comprehensive state of the science. This foundational knowledge was to be used to spotlight minimal functional performance requirements of potential agents, and importantly, to identify the evidence-based laboratory, animal, exposure, and clinical assessment methodologies that can be considered “best research practices.” In turn, adopted use of such recommendations should promote homogenous research outcomes and, thus, comparability across trials investigating new drug development.
The PIHL working group quickly concluded that any guidelines, in the strict sense of the word, would require a more thorough understanding of the field than has been conducted to date. Rigorous reviews have not been conducted which can definitively identify best practices across the spectrum of study designs in PIHL research. Therefore, in anticipation of such a systematic review, the HCE herein offers interim guidance which is the culmination of three years of working group discussion, literature review, and open dialogue during two states of the science symposia by the experts across the translational spectrum of research, including those working with front-running candidate drugs performing animal studies and clinical investigations. All discussion focused on analyzing the issues most relevant to participation in Investigational New Drug (IND) development and translation of the science for the prevention and/or rescue of hearing loss.

Simultaneously, the HCE is conducting the recommended full systematic, descriptive review of peer-reviewed PIHL studies to better understand the various elements of study methodologies being employed across the field. Using PIHL literature attained through systematic review methods consistent with current standards, the review effort will identify, characterize, evaluate and correlate the methodological variables across PIHL studies, from animal to human. This assessment will focus on the research designs in PIHL investigations, with the objective of producing conclusive, evidence-based sets of “best research design practices.” In so doing, the hope is to contribute to the current understanding of the state of the science and identify any trends across studies in this field which can refine the way toward standardization in PIHL study design. The guidances
offered in the following pages will be considered living documents, subject to updates as new evidence emerges suggesting improvements in study design practices which can further advance the field, particularly as a result of the PIHL Methodology Systematic Review project.

In all scientific disciplines, investigators are free to design their research according to their preferred style and philosophy, beholden to justify choices through literary reference when available. But when literature is as methodologically heterogeneous as PIHL literature, investigators are left to a great deal of choice. The following articles aim to provide direction by the authority of consensus not to limit investigator choices but to instill confidence and standardized justification for the choices they make. And while these views are not yet based on rigorous systematic review, the process of subject matter review, debate and experience, coupled with PIHL advisory consensus to bridge literature gaps in this developing field of research produced confident recommendations for appropriate standards, technologies or suggestions to guide future PIHL studies.

The successful consensus in the face of an interdisciplinary, inter-institutional, and competitive composition of the PIHL working group is a testament to the passion for and commitment of all involved to the advancement of the science. This broad field of experts has defined a functional way ahead that will boost the progress of everyone interested in participating in the advancement of Pharmaceutical Interventions for Hearing loss. The HCE will continue to facilitate collaborations with military study populations and establishing requirements for technology transition within the DoD. Finally, the HCE will
continue to support continual evidence-based recommendation and administrative facilitation to construct best research practices for DoD stakeholder implementation.
5.2.2 Guidelines for Auditory Threshold Measurement for Significant Threshold Shift.


URL: http://journals.lww.com/otology-neurotology/Fulltext/2016/09000/Guidelines_for_Auditory_Threshold_Measurement_for.41.aspx

Provided with permission from the publisher, Wolters Kluwer.

Abstract

The purpose of this article is to provide guidelines for determining a Significant Noise-Induced Threshold Shift in clinical trials involving human populations. The article reviews recommendations for the standards to be referenced for human subjects, equipment, test environment, and personnel. Additional guidelines for military populations are provided. Guidelines for the calibration of audiometers, sound booth noise levels, and immitance equipment are provided. In addition the guidance provides specific suggestions for the subjects history prior to study onset, and otoscopy.

Test frequencies for threshold determination and methods of threshold determination are reviewed for both air conduction and bone conduction for both baseline
testing and later determination of either a temporary (TTS) or permanent threshold shift (PTS). Once a Significant Noise-Induced Threshold Shift has been determined, subjects should be retested, conductive component should be ruled out or addressed, and the subject should be counseled or referred for additional medical evaluation. Guidance for reporting procedures and the computerized study database are described. Finally, experimental designs suggested for noise-induced otoprotection clinical trials are described.
Introduction

In general, interventional clinical trials can have a wide variety of study design approaches all within good clinical practice parameters, but pharmaceutical interventions for hearing loss (PIHL) studies have largely employed heterogenic design elements. The PIHL literature shows a broad range of design elements for clinical studies, including the intensity, duration, and type of noise exposure, dosing schedules, data collection time points, statistical analysis plans, as well as the primary audiometric endpoints. Currently, no Food and Drug Administration (FDA) guidance exists specifically for pharmacological intervention studies for hearing loss or tinnitus (FDA, 2016). However, reproducible, validated human research methodologies of the highest rigor must be employed. At a minimum, all PIHL or otoprotective clinical trials should meet International Conference on Harmonization (ICH) guidelines for clinical trials (ICH, 2016). Additionally, test equipment, test environment, clinical procedures, and personnel must meet all relevant American Speech-Language Hearing association (ASHA), American Academy of Audiology (AAA), American National Standards Institute (ANSI) standards and guidelines, and military standards where applicable. The following sections are intended to provide researchers in the PIHL field with guidance for the clinical study design elements which may eventually lead to more homogeneous and, therefore, comparable study data and outcomes.

General test environment
Audiologic testing should be conducted in a quiet testing environment meeting appropriate current standards. If testing is conducted inside a health care facility, additional requirements exist that must be met in order to maintain Joint Commission or other accreditation related to patient safety. This document focuses on recommended technical requirements.

**Sound field requirements**

Audiologic testing should be conducted inside a sound booth. Single-walled or double-walled sound booths may be appropriate depending on the ambient noise levels outside the booth, with double-walled booths providing increased attenuation relative to single-walled booths. Sound levels inside the sound room should be verified annually, or whenever any new noise source is introduced within the vicinity of the audiometric room. It is important that hearing measurements be conducted in an audiometric test room meeting specific standards because, if the ambient noise level exceeds allowable standards, the measured thresholds will be inaccurate due to the masking phenomenon. Excluding all noise from a sound room environment is generally not feasible nor required. A variety of standards specify the maximum allowable noise levels for accurate threshold assessment. In many cases, the appropriate standard will be ANSI S3.1, most recently revised in 2013 (ANSI, 2013). The current version of all ANSI standards can be obtained from the Acoustical Society of America (ASA) at http://acousticalsociety.org/standards (Acoustical Society of America, 2016).
ANSI S3.1 specifies the maximum permissible ambient noise levels (MPANLs) allowed during audiometric testing to prevent excessive ambient noise masking (American National Standards Institute, 2013). This standard is particularly relevant for clinical trials employing normal hearing listeners who may have thresholds at, or below, 0 dB HL (i.e. 0 to -10 dB HL). Importantly, ANSI S3.1 specifies different MPANLs for different test frequencies as some frequencies are more vulnerable to masking by ambient noise (ANSI, 2013). Different MPANLs are also specified for different earphone types because some earphones attenuate ambient noise more effectively than others. Within this standard, MPANLs are specified for octave and one-third octave band intervals from 125 to 8000 Hz for the audiometric conditions of testing with ears covered using supra-aural headphones or insert earphones, as well as in the free field (ears not covered). In some settings, other standards may be more appropriate. During audiometric testing conducted as part of a hearing conservation program under the requirements of 29 CFR 1910.95, the permitted noise levels in the audiometric room are increased relative to the ANSI S3.1(ANSI, 2013; OSHA, 1983). If testing is being conducted using a mobile van service, a sound-level meter will be required in order to verify sound levels meet the relevant standards once the van has arrived at the test location. Sound level meters (SLMs) must also meet the relevant specifications (American National Standards Institute, 2014). Specific performance categories define Type 1 and Type 2 SLMs, with greater measurement precision required for Type 1 (±1 dB) than for Type 2 (±2 dB) devices. A Type 2 meter is the minimum
requirement for noise measurements for OSHA purposes (OSHA, 2013). We recommend that annual professional calibrations be completed using Type 1 meters.

**Equipment standards, including calibration**

Test equipment, test environment, and test procedures must meet all relevant national standards and guidelines in the United States or the national equivalent in other countries. A variety of sources of information are available as either standards or guidelines. ANSI has established standards for audiometer performance (ANSI, 2010) as well as tympanometer performance (ANSI, 2012).

ANSI S3.6 provides specifications and tolerances for audiometers (ANSI, 2010). An important component of ANSI S3.6 is standard reference threshold levels for different earphones, as well as bone vibrators and loudspeakers. Reference Equivalent Threshold Sound Pressure Level (RETSPL) values specify the values used to convert sound levels from dB SPL to dB HL. Sound levels produced by earphones coupled to an audiometer are measured in dB SPL using microphones during the calibration process. These physical measurements are converted to dB HL, the normative reference population threshold, using RETSPLs, such that thresholds are consistently expressed in dB relative to the expected population threshold of 0 dB HL. Audiometers must be calibrated according to ANSI S3.6 at least annually, as well as anytime the equipment has been moved, to assure that threshold assessments performed on the same individual with different audiometers provide equivalent results across test sessions, and accurately represent differences between the individual’s thresholds and the normative reference thresholds (ANSI, 2010). For clinical
trial purposes, it is critically important that measurements across time accurately reflect changes in function. If clinical testing includes acoustic immittance or otoacoustic emission measurements, these devices must conform to the appropriate ANSI S3.6 specifications (ANSI, 2010).

In addition to annual professional calibration, device users should perform a daily listening check to verify equipment function. Listening checks should be used to confirm that tones are not distorted, that they are produced by both earphones and from the correct earphone, and that no background noise exceeds limits. Wires should be manipulated to ensure no intermittency that would suggest a broken wire with sporadic connection. The results of the listening check should be documented on a daily basis. If the listening check is to conform with 29 CFR 1910.95, a listener with normal, stable thresholds should be tested daily to verify that thresholds are within +/- 5 dB of the expected thresholds (OSHA, 1983). Deviations of 10 dB or greater indicate additional calibration is needed prior to use of the equipment. It is also appropriate to use a “bio-acoustic simulator” in place of a human listener as it will produce stable thresholds with no human variability. A helpful overview of calibration requirements is provided in the newly released Hearing Conservation Manual (Danielson, 2014).

Tympanometric testing is used to assess the functional status of the middle ear, in particular, the tympanic membrane and middle ear ossicles, by measuring the sound level changes of a 226 Hz acoustic stimulus as a function of dynamic pressure changes in the ear canal. Data generated include middle ear pressure (MEP), peak compensated static
acoustic admittance (\(Y_{tm}\)), and equivalent ear canal volume (\(V_{ea}\)) measurements. ANSI S3.39 provides specifications and tolerances for devices that are intended to be used for measurement of acoustic impedance, acoustic admittance, or both, based on a probe-tone frequency of 226 Hz (ANSI, 2012). Calibration of devices according to ANSI S3.39 assures that acoustic-impedance or acoustic-admittance measurements will be equivalent when tests are repeated across time, or repeated using different devices (ANSI, 2012). Although the standard is based 226 Hz probe tones, this limitation is explicitly not intended to inhibit or restrict the development or incorporation of new features including the use of probe tone frequencies other than 226 Hz. The use of higher frequency probe tones for clinical diagnosis is clearly of increasing interest (see, for example, Carazo & Sun, 2015). However, this ANSI standard does not establish normative values for human ears. Jerger and Keith (1980) advocate the use of large populations for establishing reference ranges, and normative data are available in other sources.

**Clinical Trials: Personnel, including Licensure and Certification**

When designing and conducting a clinical trial, a critical consideration is for the investigator to carefully select and monitor the personnel required to perform the work. Personnel are often the most expensive component of a clinical study, yet personnel costs can potentially be modified more easily than other fixed study costs, such as space and equipment. Unfortunately, investigators often underestimate the total number of personnel, the time commitment of the personnel to execute the clinical study, and the human resources issues such as training, vacation time, possible turnover during the study, and
sick leave. This serious mistake is common, despite the fact that study success is highly dependent upon on the motivation, effectiveness, expertise, and constant availability of the personnel workforce. These considerations apply even when the support required is minimal in nature. Over-reliance on individuals who have other full time or even part-time jobs with no official protected time commitment to the study is another common mistake of principal investigators. In military environments, military personnel generally cannot receive additional pay for their assistance in a clinical trial because they are already fully funded federal employees. Thus, a clinical trial can constitute an extra uncompensated workload for them in addition to their regular duties. It is critical to have committed and funded individuals to successfully navigate the “trials” of any PIHL clinical trial as documented in this article.

In order to conduct this type of a trial, certain skill sets among study personnel are required as detailed below. While it may seem economically feasible to budget and plan for individuals to fill multiple roles, it is highly recommended that PIHL studies are planned with a minimum of one individual with distinct experience and expertise in each of these areas although some may be part time (e.g., the PI or statistician). With each personnel type listed, we will define the jobs they can perform and the necessary certification and/or licensure.

**Principal Investigator (PI)**

The Principal Investigator (PI) has overall responsibility for all elements of the clinical trial including study design, regulatory reviews and approvals, study
implementation, recruitment, enrollment, study procedures (from consent to experimental elements), scientific analysis, and scholarly presentation as well as any reporting requirements associated with institutional, regulatory, or funding agencies. Given this range of responsibilities, the PI must have the proper background, experience, time, and credentials to carry out these many different roles. For clinical trials in hearing loss, this individual is usually an Otolaryngologist (with potentially a further sub-specialization in Otology/Neurotology) or a PhD (in Audiology or Neuroscience).

**Lead Study Coordinator or Project Director**

Most investigators experienced in clinical trials will agree that the individual most important to the success of the clinical trial is a good Clinical Research Coordinator (CRC) or Project Director (PD). This lead individual is responsible for all the administrative elements of the trial including compiling study submission documents such as the Investigator’s Brochure, Clinical Protocol and Case Report Forms, monitoring study document submissions and IRB approval, implementing all monitoring systems for the study, recruiting and tracking study participants, and, in many cases, staff management. If the clinical trial is a multi-center study, the responsibilities of the lead CRC, PD or study director would involve coordinating these and a myriad of other elements at each separate site. Preferably, these individuals will have a Masters or higher degree in Public Health (MPH), Nursing, or other related/relevant field with additional training specifically in research and study coordination, design, and monitoring and certification from a nationally recognized organization such as the Society of Research Administrators International.
(SRA), Association of Clinical Research Professionals (ACRP) or The Society of Clinical Research Associates (SoCRA).

**Research Audiologist(s)**

The audiologist is the backbone of any clinical study involving hearing and is responsible for working with the PI and study coordinator on study design and implementation, and is the individual with day-to-day oversight of all hearing measures or auditory assessments in the study. The audiologists will be responsible for all testing and for recording the audiologic data files for all patients enrolled in the study. Given that study outcomes are dependent upon data collected by the audiologists, it is critical that these individuals have a significant amount of experience with clinical and research audiology and have appropriate time to dedicate to the project. In general, individuals in this role will have a doctorate in audiology (AuD); however, if they were licensed prior to the adoption of the AuD as the terminal degree in Audiology, they may have a master’s degree in audiology combined with completion of a fellowship from a graduate program accredited regionally and by ASHA. In many cases, a PhD audiologist may be desirable for at least the lead audiology role to ensure that the rigorous standards of research are appropriately focused upon and prioritized. However, the PhD audiologist should also have a solid clinical background including not only clinical training and licensure but extensive clinical experience. In the US, every state has an audiology licensure, so employing licensed audiologists is required for clinical practice and should be standard for clinical trials. For other countries, testing should be conducted by the equivalent personnel in the host country.
recognizing that in other countries, trained audiometric technicians may be the most skilled and appropriate personnel delivering the audiologic standard of care in that country. Further, it is incumbent on the study team to assure that all staff responsible for audiological testing in foreign-speaking nations both fully understand the protocol and ensure that language barriers do not introduce study variables.

**Audiology Technician(s)**

In addition to a team of audiologists that collect the audiometric data, PIs may choose to rely on audiology-trained technicians to carry out certain day-to-day elements of the study under the supervision of the study audiologist and PI. These individuals should be dedicated to the study, and if the individual is part-time, the portion of their time devoted to the study must be carefully specified and monitored. Certification for this individual can be difficult to accurately define. Local IRB certification requirements may vary by institution and by study type (i.e. single vs multi-center), local and national audiology requirements, and device specific certification. State licensure laws for audiologists and audiology technicians may also be a factor. The number and qualifications of the individuals required on the study team will depend on the study size and the timing of interventions/observations and other human resources factors such as vacation time and overtime calculations.

Certain study design elements, such as subject screening for further audiology follow-up testing or longitudinal study follow-up, may warrant testing performed by technicians who are certified by the Council for Accreditation in Occupational Hearing
Conservation (CAOHC) and under the supervision of an audiologist. For studies including military personnel as subjects specifically for noise-induced hearing loss monitoring, the overarching regulation for testing is the Department of Defense Instruction (DoDI) 6055.12 Hearing Conservation Program (HCP) dated 3 December 2010 (DoD, 2010). Section 9(b)(1) states that all hearing conservation audiometric surveillance testing shall, "Be performed by a licensed audiologist, otolaryngologist, or other qualified physician; or by a technician who has attended training approved by the Council for Accreditation in Occupational Hearing Conservation or equivalent military training. A technician who performs audiometric tests shall be responsible to an audiologist, an otolaryngologist, or other qualified physician."

**Study Technician**

Depending on the size of the study and the elements of audiology testing/equipment being used, an additional study technician or technicians may be necessary to help with study procedures other than audiologic testing. While using technicians is not often necessary, a good technician with a variety of skill sets can keep equipment up and running and the study on target in a variety of situations. However, for studies involving more challenging audiologic test populations such as pediatrics, geriatrics, disabled or ill patients, testing should be performed by an audiologist for US studies or the most qualified individual appropriate in other countries.

**Biostatistician**
A study statistician is a critical element of any study team and is involved in study design, determination of statistical methods for analyzing the data, power analysis, and the scholarly presentation and publication of the study data. If not a biostatistician by trade and degree, this individual should at least have extensive research experience in hearing as well as an advanced degree with a focus or emphasis in biostatistics, which may be represented across a variety of scientific disciplines.

Clinical Trials: Procedures for Pure Tone Threshold Testing:

Regardless of study design, audiological exams ought to include a detailed history including any preceding noise exposure and the use of hearing protective devices (HPDs), and whether additional complaints of aural pain, fullness, pressure, or tinnitus are present. A physical examination including otoscopy needs to be conducted with the appearance of the ear drum and any defects or abnormalities of the external ear canal noted. Evidence of middle ear disease including tympanic membrane perforation, retraction or other deformity requires further medical evaluation by an otolaryngologist. An audiometric examination should include tympanometry, a non-invasive test of middle ear function, and conventional pure-tone air and bone conduction audiometry: behavioral tests of hearing threshold that can identify and characterize conductive, mixed and/or sensorineural hearing loss, should be completed.

Pure-tone air conduction threshold testing should be conducted both at baseline and after the noise exposure or within two to four weeks post noise, to determine whether a
TTS or PTS exists. Pure-tone air-conduction testing should be conducted at 0.5, 1, 2, 3, 4, 6, 8 kHz. Several studies have included threshold tests in the extended high frequency (EHF) range (> 8 kHz); the utility of EHF testing in PIHL trials has not been confirmed and is not recommended as an essential part of PIHL clinical trials. However, if time and budget allow, EHF testing could become an interesting element for meta-analyses in the future. Bone conduction testing should be conducted at 0.5, 1, 2, 3, and 4 kHz if the pure tone air-conduction threshold at that frequency is greater than or equal to 15 dB HL.

Pure-tone threshold testing should be conducted using the modified Hughson Westlake procedure (Carhart & Jerger, 1959; American Speech-Language-Hearing Association, 1977) as follows: Initial descent towards threshold is accomplished in 10-dB steps. Beginning with the first non-response, level is increased by 5-dB for each non-response, and decreased by 10-dB after each correct detection response. Threshold is defined as the lowest level at which two responses are obtained out of three presentations on an ascending run.

At the baseline visit, pure-tone air-conduction testing should be immediately repeated at 1 and 2 kHz to determine that the subject provides reliable responses. Responses are considered reliable if retest thresholds at both frequencies do not exceed ± 5 dB of the previously obtained threshold response. This method of verifying threshold reliability in clinical populations is based on ototoxicity monitoring protocols described by Fausti, et al. and Campbell et al. (Fausti, 1999; Campbell, 2003).
The timing of the baseline and follow-up tests may vary by study. Clinically, for acute acoustic trauma inclusion studies, an individual presenting clinically with a complaint of hearing loss, aural pain or tinnitus needs to be evaluated as soon as possible to determine the extent of the injury and to provide a diagnosis and prognosis.

Although not measures of auditory threshold, otoscopy and tympanometry, just prior to each hearing assessment, are advisable to rule out possible outer or middle ear abnormality. Unidentified outer or middle ear disorders may cause air conduction threshold abnormalities or fluctuant hearing thresholds unrelated to noise exposure. Thus, subjects presenting with potential conductive disorders should be excluded from participation in PIHL clinical trials to avoid incorrect data interpretation later.

Tympanometry should be measured with a standard 226 Hz probe tone generally with a pressure sweep from +200 to -400 daPa. Standardized criterion for pass/fail should be set for the clinical trial.

For clinical trials, or to standardize procedures across sites, tympanometry screeners can provide fast, easy and standardized measures with a simple “pass” or “fail” determination. These screeners are particularly useful if audiometric technicians are employed in the data collection process.

**Determination of TTS, PTS and Otoprotection**

Pure tone audiometry is the criterion standard by which sensorineural hearing loss especially NIHL is determined. The conventional audiogram illustrates hearing thresholds
at several different test frequencies from 0.5 to 8 kHz in each ear, independently. A typical audiogram from a patient with NIHL will show a greater loss of hearing sensitivity at 3, 4 or 6 kHz vs 0.5, 1, 2 and 8 kHz; this configuration is commonly referred to as a “notched” audiogram. A temporary change in hearing sensitivity or threshold shift (TTS) occurs and recovers within hours to days of the noise exposure, typically 16-48 hours (Kirchner et al., 2012). During this period, one’s ability to discriminate speech might be impaired and the perception of tinnitus is sometimes reported. A permanent change or loss in hearing sensitivity or threshold shift (PTS) is confirmed with an audiometric re-test at least three weeks, preferably 30 days, after the noise exposure. The majority of temporary loss resolves within a few days after noise exposure, but hearing can continue to gradually improve. The risk of PTS usually begins with hearing loss persisting at 14 days after noise exposure with the upper limit of recovery being 30 days. However TTS and PTS outcomes may vary by noise insult and patient factors. Prior to each audiologic assessment for PTS the patient should have a quiet period or lack of noise exposure in the 16-24 hours immediately preceding the audiometric exam but that quiet period before testing is not required to determine TTS. TTS (H93.24) and PTS or NIHL (H83.3) have specific ICD-10 classifications and should be coded appropriately. Additional comorbidities such as tinnitus (H93.1) or hyperacusis (H93.23 a sensitivity to sound) may also be reported by the subject and should be documented as well.

A significant and clinically relevant loss of hearing occurs when a $\geq 10$ dB loss of hearing sensitivity or threshold shift has been demonstrated, at one or multiple test
frequencies. In the work place, OSHA has established the standard threshold shift (STS) criteria, which means that a $\geq 10$ dB average threshold shift occurred at 2, 3, and 4 kHz in the same ear (OSHA, 1983). When this shift is confirmed by a re-test, the pure-tone average threshold exceeds 25 dB HL, and the hearing loss is not secondary to recreational noise exposure or other non-occupational factors, then an STS has occurred. STS is considered a significant work related injury (WRI) and must be reported. STS or WRIs are often used to monitor hazardous work areas or conditions and should be used to further improve hearing conservation programs. Unfortunately, many initial STS or PTS that are $\geq 10$ dB are not reported because they do not satisfy this WRI rule. For example, a threshold shift of 0 dB at 2 kHz, 10 dB at 3 kHz and 15 dB at 4 kHz would average 8.3 dB across 2, 3 and 4 kHz in the same ear; retest would not be required and hearing loss would not be reported. OSHA only requires the reporting of an STS. Changes in 6 kHz hearing are not averaged at all in the determination of an STS, even though TTS and PTS at 6 kHz hearing are frequently observed in noise exposed individuals (OSHA, 1983). The Department of Defense guidelines: Defense Occupational and Environmental Health Readiness System-Hearing Conservation (DOEHRS-HC) guidelines use the same standard for determination of STS as does OSHA, In addition the guidelines provide a guidance for early warning shift STS or early warning flag, which is defined as a 15 dB or greater change at 1, 2, 3, OR 4 kHz in either ear (DoD, 2010).

Hearing protective devices (HPDs) and other environmental engineering controls are two important and critical instruments or processes of an effective hearing conservation
program that reduces an individual’s noise exposure and risk of developing either a noise
induced TTS or PTS. Any research study aiming to prevent or rescue a noise injury must
be able to demonstrate that investigators have taken all precautionary measures, including
but possibly above and beyond OSHA mandates, to protect the study participants. OSHA
mandates a hearing conservation program including annual audiometric testing be put in
place in work environments where the noise exposure reaches or exceeds 85 dBA based on
a time weighted average (TWA) over an 8-hour work shift (OSHA, 1983). Adequate HPDs
must be provided to workers in hazardous or noisy work environments where their
individual noise exposure exceeds 90 dBA TWA. Noise exposures or TWAs are
determined using sound level meters in the immediate work environment or by personal
dosimeters mounted at the shoulder.

For the purposes of this discussion, we will limit the definition of otoprotection to
pharmacologic strategies or drugs that aim to reduce, mitigate, prevent or treat a NIHL.
Recent research has demonstrated several changes in both sensory and neural processes
underlying a noise-induced TTS or PTS. The sensorineural changes observed in the noise-
induced TTS and PTS often involve the same cell types such as auditory hair cells and
neurons. One difference is that auditory hair cell and neuronal cell death or apoptosis
clearly result in a loss of hearing sensitivity, while lesser auditory hair cell and neuronal
injury may not result in a loss of hearing sensitivity. At least 50 potential otoprotectants
have been tested in several different preclinical models of TTS and PTS (for reviews, see
Lynch & Kil, 2005; Campbell & Le Prell, 2012, Le Prell & Bao, 2012). Typically, these
investigational drugs have been injected into laboratory animals such as mice, rats, guinea pigs, or chinchillas, prior to and after the noise exposure. Only a few of these animal studies have delivered the otoprotective drugs orally and/or after the induction of an NIHL. The drugs that have demonstrated the most effective preclinical otoprotection display either anti-oxidant, anti-inflammatory or anti-apoptotic properties. While no otoprotective drugs have been FDA approved, several drugs have been tested in man or are in active clinical testing for this indication in an affected population.

Effective otoprotection should be defined as including a significant reduction in the incidence and/or severity of either the TTS and/or the PTS. Several clinically validated measures would be considered important determinants of either a TTS or PTS, such as pure tone audiometry at 3, 4, and 6 kHz and/or word recognition tests. Although not direct determinants of TTS or PTS, patient reports of tinnitus or hyperacusis may also be a consideration. In the case of an acute or single noise exposure, a reduction in the incidence, severity or duration of the TTS would be considered significant and potentially clinically relevant. For example, a reduction in the incidence of a $\geq 10$ dB threshold shift would be considered significant and clinically relevant, since a 10 dB loss in hearing sensitivity requires a 10 fold increase in sound intensity to evoke an accurate behavioral response using pure tone audiometry. A 10 dB improvement in hearing sensitivity would potentially allow for better word recognition in the acute period especially in a noisy environment where the signal to noise ratio is low ($\leq 6$ dB). A reduction in the duration of the TTS (e.g. from days to hours) would also be considered a clinically relevant improvement in hearing.
In the case of chronic or repeated noise exposure that results in a PTS, a reduction in the incidence or severity of the PTS would be considered highly significant and clinically relevant. In the case of chronic NIHL, a reduction in the progression of a PTS would be considered significant and clinically relevant. Acute NIHL (TTS) has been linked to increased or accelerated Age-Related Hearing Loss (Kujawa and Liberman, 2006), although this outcome is not observed after all exposures resulting in TTS (Fernandez et al., 2015). A clinically relevant improvement in hearing or effective otoprotection would reduce the incidence, severity of duration of the noise-induced TTS or PTS, and may have the potential to prevent accelerations in Age-Related Hearing Loss.

**Study Design and Data Capture**

Experimental design consists of within-subjects serial testing in which baseline standard frequency audiograms (as outlined above) are initially acquired. By comparing similar measures obtained at the end of the study period to the relevant pre-noise exposure or baseline audiogram, reliable noise-induced changes in pure-tone hearing threshold can be identified. Thus, subjects will serve as their own control for identifying a specific change in hearing based on frequency and ear.

The generally accepted criterion standard design to prove safety and efficacy of a pharmaceutical agent is the prospective, double-blind, placebo-controlled Randomized Controlled Trial (RCT), reviewed and approved by an IRB for human subjects protections.
considerations. In order to accomplish this in a PIHL investigation, several study elements must be considered.

First, the manufacturing of the investigational agent must be carried out with the forethought to fully blind both the study subjects and the investigators. Active and placebo batches need to appear as identical as possible (i.e. size, shape, color, taste). Differences between active and placebo batches perceived by either study subjects or the clinical investigators may introduce a bias which, if detected during the conduct of the study, should be reported. PIs should familiarize themselves with the Current Good Manufacturing Practice regulations (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm090016.htm) at the forefront of study design (FDA, 2016).

Second, the experimental design itself must be considered. Previous hearing loss clinical trials have employed within-subjects serial testing in which baseline standard frequency audiograms (as outlined above) are initially acquired and then compared to measurements obtained at the end of the study period at a single site. For example, in Kopke et al. (2015) investigators determined significant noise-induced changes in pure-tone hearing threshold by collecting a baseline audiogram (per guidance above), followed by 16 days of weapons training, followed by another audiogram in the same booth, with the same equipment, 10 days after the last noise exposure. The goal of this interventional study was to determine if n-acetylcysteine (NAC) could prevent NIHL among US Marine Corps recruits stationed at the Marine Corps Recruit Depot (MCRD) in San Diego, CA.
The investigators found that even in monitored HPD-protected subjects, at least 27% of placebo subjects experienced a threshold shift; thus, demonstrating that subjects can adequately serve as their own control for identifying a significant hearing change due to active military training.

In the prevention indication studies to date, the investigators follow cohorts through similar pre-planned noise exposures, using actual or estimated rates of hearing loss based on those specific noise exposures to calculate an appropriately powered clinical trial. However, in a treatment indication study, the investigator will be faced with fluctuating rates of hearing loss, changes in the duration or severity of the hearing loss, and the timing and/or the reporting of the injury by the subject. Therefore, in a trial designed to test a treatment indication, the prospective plan will likely need to expand beyond a single site.

NAC was also tested in a treatment indication study, which involved four US military base installations. This multi-center, prospective, randomized, double-blind, placebo-controlled study began the dosing of NAC or placebo for 7 days within four hours of an acute acoustic trauma as documented by audiologic inclusion criteria. The self-report feature of the study design ultimately led to its failure to enroll subjects and the study closed before any significant data was collected. It is imperative that investigators consider such design limitations and employ both reasonable expectations as well as, whenever possible, pilot studies to test the logistics of any study design plan. The success of any prevention or treatment indication trial design will hinge on the rates of injury, the duration of the hearing loss, and timely access to that affected population.
Two additional crucial elements of the study design itself are the noise exposure or otherwise injury-imposing exposure(s) anticipated from which to protect or treat, as well as the timely access to such identified study populations. The primary challenge of the former element is that PIHL research, like other areas of research such as infectious diseases and chemical and biological warfare injury, aims to test a population with a potentially permanent disabling injury (Gronvall et al., 2007). Like researchers in anthrax or smallpox, PIHL researchers must consider ethical and feasible limitations of human safety and efficacy trials. If a population is identified which will predictably sustain a permanent or chronic NIHL, there is a moral imperative to introduce protective efforts to prevent it. Moreover, an investigator should not intentionally impose a PTS or chronic NIHL on any human population. Thus, researchers are left searching for plausible-yet-unknown exposures within which to test an otoprotectant. And if permanent injuries are identified through the auditory measurements captured, follow-up procedures must be in place both to treat the studied cohort and to better protect future cohorts within that population. Ideally, to accomplish the former, a computerized study database should be configured so that when the post-noise audiogram is entered in the database, criteria for hearing change will automatically be calculated and flagged, so that the examiner can recheck the frequencies in question and refer for follow-up standard of care for those affected subjects. Appropriate Hearing Conservation Programs ought to be consulted to accomplish the latter.
While identification of a viable study population has its unique challenges in PIHL research, gaining access to that affected population within study design parameters (i.e. hours) may prove to be among the most challenging aspects of the clinical trial. Timing and space requirements for testing as outlined above may not coincide with ideal trial design elements. For example, location of audiometric testing booths may require clinic space far from the location of noise exposure which may impede ability to test within a certain window pre- or post-exposure. There may also be issues with securing appropriate study testing space in traditional medical treatment facilities which lack dedicated research space. Further obstacles to population access need to be accounted for during study planning, a particularly important aspect in military population studies where population access may include physical access issues like base installation passes; vulnerable population regulations requiring absent senior ranking officials and present ombudsman for subject protections; or waivers from subjects’ commanding officers to participate at all.

True to all RCTs, investigators ought to take care in capturing any confounding elements of noise exposure including concomitant medications, smoking and drinking habits, environmental exposures to solvents or other noise sources, and intermittent use of HPDs. Finally, data capture and quality assurance must be considered. Electronic records may not be available in all cases and anticipating the task of comprehensively combing medical records for pertinent study data elements is critical.
5.2.3 Temporary and Permanent Noise-induced Threshold Shifts: A Review of
Basic and Clinical Observations

Ryan, Allen F.; Kujawa, Sharon G.; Hammill, Tanisha; Le Prell, Colleen; Kil, Jonathan.
Temporary and Permanent Noise-induced Threshold Shifts: A Review of Basic and
Number: 10.1097/MAO.0000000000001071.

URL: http://journals.lww.com/otology-neurotology/Fulltext/2016/09000/Temporary_and_Permanent_Noise_induced_Threshold
.42.aspx

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Abstract

Exposure to intense sound or noise can result in temporary increases in hearing
thresholds or in permanent hearing loss. In the latter case, a loss that is apparent
immediately after exposure does not recover to pre-exposure hearing levels. Acute changes
in hearing sensitivity are known as temporary threshold shift (TTS), while chronic deficits
in sensitivity are termed permanent threshold shift (PTS). In general, a 10 dB or greater
threshold shift at 2, 3 and 4 kHz is required for reporting purposes in human studies. As
in many forms of hearing loss, the high-frequency, basal regions of the cochlea are more
sensitive to noise damage than the apex. In addition, resonance of the ear canal results in
a frequency region of high sensitivity to noise at 4-6 kHz. A primary target of intense noise
is the cochlear hair cell. While the mechanisms that underlie noise-induced hair cell
damage remain unclear, there is evidence to support a role for reactive oxygen species,
stress pathway signaling and apoptosis. Another target of noise is the synapse between the
hair cell and the primary auditory neurons of the spiral ganglion. Large numbers of these
synapses and their neurons can be lost after noise, even though hearing thresholds may
return to normal. This in turn affects auditory processing and the detection of signals in
noise. The consequences of TTS and PTS include significant deficits in communication
that can impact performance of military duties or obtaining/retaining civilian employment.
Tinnitus and exacerbation of post-traumatic stress disorder are also potential sequelae.

**Definition of Temporary and Permanent Threshold Shifts**

Hearing loss due to noise has been recognized in humans for centuries (Thurston,
2013). However, it was only in the 20th century that the phenomenon of noise-induced
hearing loss (NIHL) was rigorously investigated in animals, allowing a more accurate
determination and definition of the disease. Such studies have demonstrated that exposure
to excessive sound produces hearing loss (threshold sensitivity loss), with the magnitude
of the initial shift and the degree of recovery depending on characteristics of the exposure
in the level, time and frequency domains, and on characteristics of the individual, as noted
below. Threshold shifts that recover to baseline levels in the hours, days or weeks following
exposure are termed temporary threshold shifts (TTS). More injurious exposures can
produce threshold sensitivity losses containing both temporary and permanent components,
in which the majority of the TTS resolves but a measurable permanent threshold shift (PTS) has evolved (e.g. Eldredge et al., 1973; Ryan and Bone, 1976). Threshold shifts of up to ~50 dB immediately after a single noise exposure may recover completely, while more extensive immediate hearing losses are likely to result in permanent losses of hearing sensitivity (e.g. Ryan and Bone, 1976; Clarke and Bohne, 1999). Continuous or repeated exposures to noise that only induce a TTS, may evolve to a PTS if repeated (Lonsbury-Martin, 1987), as occurs in occupational noise exposure. Therefore, PTS can be defined as noise-induced threshold shift that persists after a period of recovery subsequent to the exposure. In animal models, recovery has been reported for periods extending up to 3 weeks, therefore it may be premature to define a threshold shift as temporary until at least 3 weeks post-exposure, when a permanent threshold shift arises.

While the smallest level of TTS or PTS that can be reliably measured in an individual has not been well defined given test-to-test variability in individuals, several standards have been set for what is considered a significant hearing loss or “standard threshold shift” (STS). The Occupational Safety and Health Administration (OSHA) states that an STS is a 10 decibel (dB) increase in hearing threshold averaged across 2000, 3000 and 4000 Hz in the same ear from an individual’s baseline or recent annual audiogram (29 CFR 1910.95). An STS is a reportable work related injury once it has been reconfirmed with a retest within 30 days of the initial test and results in a hearing threshold of at least 25 dB in the affected ear. Therefore, most occupational hearing loss or PTS is under reported since OSHA only requires an STS to be reported.
The Department of Defense (DoD) policy for the military’s Hearing Conservation Program (HCP) and the American Speech-Language-Hearing Association (ASHA) similarly define STS by a 10 dB shift average using the same frequencies, “in either ear without age corrections” (DoDI 6055.12, 2010 [currently under revision]; ASHA, http://www.asha.org/public/hearing/Degree-of-Hearing-Loss/, 2015). In contrast, the National Institute of Occupational Safety and Health (NIOSH) recommended definition of an STS is “an increase of 15 dB in hearing threshold level (HTL) at 500, 1000, 2000, 3000, 4000, or 6000 Hz in either ear, as determined by two consecutive audiometric tests,” with the second test required to reduce false-positive findings (NIOSH 98-126, 1998). A significant negative STS (improved hearing) is further defined by the DoD as a decrease of 10 dB or greater change (improvement in hearing) for the average of 2, 3 and 4 kHz in either ear. An early warning shift STS (decrease in hearing) is defined as a 10 dB or greater change at 1, 2, 3 or 4 kHz in either ear. Therefore, a consistent measure between TTS and PTS involves a 10 dB shift from baseline hearing involving one or more frequencies in the same ear.

Characteristics of PTS

PTS is sensorineural and varies across frequencies, depending on characteristics of the exposure, the transmission characteristics of the external and middle ears, and the innate sensitivity of different regions of the cochlea to damage.
Noise damage is typically most extensive at frequencies above those of the exposure (Cody and Johnstone, 1981), a phenomenon well explained by nonlinearities in the cochlear mechanical response to sound (Robles and Ruggero, 2001). This is most apparent for TTS and for low levels of PTS. However, noises to which human ears are exposed often are broadband in frequency composition. These signals are shaped (some frequencies amplified, others reduced by filtering) by passage through the external and middle ears (Rosowski, 1991). Resonance in the ear canal produces amplification of acoustic frequencies whose wavelengths are approximately 4 times the length of the canal, which for humans results in enhancement of frequencies around 4 kHz. This contributes to an enhanced “notch” of PTS at 4-6 kHz for exposure to broad-band stimuli. Finally, as with many other forms of damage, the basal cochlea appears to be most vulnerable to noise. While the reason for this is not entirely clear, it may be related to higher levels of antioxidants in apical hair cells as well as higher rates of metabolic activity in basal hair cells (Sha et al., 2001). This basal sensitivity results in a tendency for TTS and PTS to be more extensive at high frequencies.

**Characteristics of TTS**

TTS is a change in hearing threshold that recovers to pre-exposure levels (baseline) over time. The amount of time to recover to baseline may be relatively fast (minutes to hours) or slow (days to weeks). The severity of the initial insult, as well as the time course of the recovery, are dependent on a number of factors including: the type of insult or...
trauma, the intensity and duration of the insult (single vs repeated, short vs long exposures), and the stimulus type (impulse/impact sound or continuous noise including wide or narrow-band noise). Individual susceptibility is dependent on the use of hearing protective devices, the quiet time or rest between exposures, and the level of hearing loss prior to exposure. Individual susceptibility to TTS may also be influenced by age, sex, prior history of noise exposure, diabetes, genotype and other personal or environmental factors such as smoking and diet. While these factors are at play for PTS as well, unlike PTS, TTS is a change in hearing sensitivity which recovers to baseline or within test/retest criteria in minutes, hours, days or weeks with the upper limit being 30 days post exposure. TTS and PTS outcomes will vary as a function of the insult and individual factors.

**Mechanisms of TTS**

Historically, TTS was largely thought to be a mechanical process that involved structures within the outer and middle ear including the ear drum, ossicular chain and middle ear muscles through the acoustic reflex. Extremely intense noise exposure is also known to mechanically damage the cochlea, disrupting the connections between the tectorial membrane and outer hair cell stereocilia, damaging the stereocilia themselves, breaching the integrity of the reticular lamina or even disrupting the basilar membrane.

However, recent work in several preclinical studies has demonstrated a significant involvement of several sensorineural inner ear structures including hair cells and their stereocilia, supporting cells within the organ of Corti, endothelial cells and fibrocytes within
the stria vascularis and spiral ligament, and dendritic processes of the auditory nerve (Mulroy et al., 1990; Kujawa and Liberman, 2009). Molecular and biochemical changes have been identified that include pro-inflammatory and pro-apoptotic processes (Henderson et al., 2006). These changes have been shown to alter the normal function of several critical processes within the cochlea including the endolymphatic potential that drives hair cell depolarization (Yan et al., 2013), cellular membranes and mitochondria responsible for hair cell and supporting cell activity, and neural innervation of the inner hair cell that conduct impulses to the auditory brainstem. In addition, changes in the activity or metabolism of neurons in the cochlear nucleus, superior-olivary complex and inferior colliculus have been observed (Ryan et al., 1992). In support of this noise-induced change in inner ear biology and pharmacology and its relevance in establishing the TTS, several preclinical studies have demonstrated a significant reduction in TTS when the animals were administered otoprotective compounds or drugs immediately prior to noise exposure (Siedman et al., 1993; Attias et al., 2004; Yamasoba et al., 2005; Lynch and Kil, 2005; Kil et al., 2007).

Mechanisms of PTS

While intense sounds such as blast can damage the conductive apparatus of the outer and middle ears, producing permanent hearing loss through tympanic membrane rupture or ossicular dislocation, PTS is generally considered to be a sensorineural phenomenon restricted to the cells of the cochlea. The most recognized cause of PTS is damage to and loss of cochlear hair cells. The mechanisms by which this damage can occur are not known.
with certainty. However, there is extensive evidence implicating the generation of reactive oxygen species (ROS) within hair cells during and after overexposure (Henderson et al., 2006). This leads to the activation of stress signaling pathways such as the JNK MAP kinase cascade (Pirvola et al., 2000), which can in turn lead to cell damage, apoptosis and/or necrosis (Bohne et al., 2007). The biochemical pathways leading to hair cell damage/death are undoubtedly complex, and also appear to include competing survival pathways that attempt to rescue hair cells and restore their function. It is the balance of these competing pathways that determine the fate of the cell. The outer hair cells, responsible for the exquisite sensitivity and frequency and selectivity of the cochlea, are the most sensitive to damage (Eldredge et al., 1973; Ryan and Bone, 1976).

Noise also can target hair cell synapses and neurons directly, even when the hair cells themselves remain and recover normal function. The insult is seen acutely as a glutamate-like ‘excitotoxicity’ that includes swelling and retraction of afferent terminals from beneath inner hair cells (Robertson 1983). Recent work in animal models shows that noise-induced loss of synapses and afferent terminals is rapid and permanent (Kujawa and Liberman 2009; Lin et al 2011). Loss of spiral ganglion neurons is comparatively slow, and can be ‘primary,’ that is, occurring without noise-induced hair cell loss (Kujawa and Liberman 2006; 2009; Lin et al 2011) or ‘secondary’ to the loss of their inner hair-cell targets (Bohne, 1997; Puel, 1998). Such synaptic and neural loss can exacerbate the functional consequences of noise exposure by reducing the ability of the VIIIth nerve to encode auditory signals with fidelity, with or
without loss of threshold sensitivity (Bharadwaj et al 2014). Thus, lack of PTS does not imply that auditory function is normal.

It should be noted that our understanding of the mechanisms of NIHL remain incomplete. For example, many of the processes that have been proposed to mediate hearing loss would take considerable time to develop. However impulse exposures, even those that do not result in PTS, produce hearing loss essentially instantaneously, without immediate loss of cells. Presumably this represents a disruption of cochlear cells at the microstructural and protein levels. In another example, it has recently been suggested that the initial 10-15 dB of TTS may serve as a mechanism to extend the dynamic range of hearing, rather than representing a damage mechanism (Housley et al., 2013). Finally, noise exposure that accumulates over a lifetime of occupational exposure may well involve different processes than more acute damage (Kirchner et al., 2012). Further studies of NIHL mechanisms are clearly warranted.

**Consequences of PTS**

ASHA uses the following threshold-based definitions of hearing loss: none (normal hearing) (-10-15 dB), slight (16-24 dB), mild (25-40 dB), moderate (41-55 dB), moderately severe (56-70 dB), severe (71-90 dB), or profound (>91 dB). Thus, 10 dB of PTS would have different consequences depending upon the initial level of hearing, for example leaving one individual with normal hearing (by definition) while increasing hearing loss from mild to moderate in another. One reasonable strategy may be to calculate the resulting
hearing handicap as per the American Academy of Otolaryngology (AAO) 1979 criteria, or using the ASHA criteria, both of which incorporate a low fence of 25-dB HL. Key differences include the frequencies included in the calculation (AAO-1979: 0.5, 1, 2, and 3 kHz; ASHA: 1, 2, 3, and 4 kHz) and the growth rate for impairment for PTA thresholds above the low fence value (AAO-1979: 1.5% per dB; ASHA: 2% per dB). However, if PTA thresholds were below 25 dB HL after the exposure, the PTS would be “missed” using this scheme, as there is deemed to be no handicap below the low fence value. Moreover, functional losses that have no threshold change correlate would not be recognized using these strategies.

The consequences of threshold sensitivity loss have been well documented in animal studies of auditory physiology and psychophysical studies of human auditory function. Loss of 40 dB of hearing sensitivity is associated with a loss of outer hair cells, which as noted above are responsible for the lower ranges of hearing sensitivity, and for the sharply tuned responses of the cochlea to individual frequencies. The loss of these cells leads to a degraded ability to discriminate sounds, especially in noisy environments. More severe hearing loss is associated with the loss of inner hair cells, which transmit sensory information from the cochlea to the central auditory system. In addition, a rearrangement or loss of the adjacent supporting cells including Hensen’s cells, Dieter’s cells and inner and outer pillar cells may contribute to further impairment or loss of passive amplification. Loss of all inner hair cells from a cochlear region eliminates auditory response, and loss from the entire cochlea results in total deafness.
Of course, the consequences of PTS are dependent upon the degree and frequency range of the loss and total loss of hearing from noise exposure is rare. However, with PTS leading to moderate and especially severe hearing loss, many facets of life become extremely challenging (Arlinger, 2003). Communication is significantly impacted. This can lead to difficulty in performing military duties or in obtaining/retaining civilian employment. Social interactions are also heavily impacted, with the result that individuals with hearing loss can become withdrawn and isolated. This can in turn lead to depression and possibly cognitive decline (Arlinger, 2003). In the case of blast injury, hearing loss can exacerbate the effects of traumatic brain injury (TBI), even when TBI is mild (Lew et al., 2009). Another consequence of noise exposure is an increase in sensitivity to other forms of hearing loss, including ototoxicity (Bone and Ryan, 1978) and aging (Campo et al., 2011).

There is also a strong, positive correlation between the presence of noise-induced permanent hearing loss and tinnitus (Mazurek et al., 2010). While tinnitus can be a benign condition, a large fraction of individuals with tinnitus experience distress that can be extreme (e.g. Gomaa et al., 2014). A lesser correlation is observed for hyperacusis (e.g. Jansen et al., 2009), another negative sequela of PTS.
5.3 **HEARING RESEARCH SPECIAL ISSUE: NOISE AND THE MILITARY**

The second special issue endeavor was published by the Hearing Research, a journal that publishes basic and translational auditory research. The issue is comprised of 23 articles, including the co-authored editorial introduction. The articles are divided into two sections – the first focusing on the scope of the problem of hearing injury, noise exposure, and solutions within the military environment, and the second dedicated to the exploration of current state-of-the-science in mechanisms of action and targets for intervention along auditory injury mechanical and metabolic pathways.

Contributing to the execution of Primary Aim 2 – to grow relationships and dialogue between stakeholders at federal agencies wherein creative solutions to PIHL research problems can be addressed – the paper in section 5.3.2 below describes the history of FDA policy process and evolution (Hammill, 2016). Writing this paper created occasion for dialogue with the FDA members of PIHL. While PIHL group-devised and -endorsed BRPs may be adopted by the FDA for study design requirements, the problem of how to more quickly advance clinical trials without accessible clinical trial populations which experience adequately sized acoustic injuries remains a major obstacle. The myth of a rigid FDA is challenged in this paper and instead a compassionate agency with the intentions and authority to solve new challenges is presented.
5.3.1 Guest Editorial – Volume Introduction


Noise induced hearing loss (NIHL) and tinnitus, often co-existing conditions, are both complex auditory deficits. These issues are being faced on a global scale, in both the military and civilian sectors. We, the guest editors, have assembled a collection of original research manuscripts and reviews that we hope will provide the readers with insights into the demands of military operations and training and the resultant stress placed on the auditory system. To counter those stresses, the United States military has invested significantly in research projects that, in the long run, will benefit both the military and civilian sectors. The purpose of this special edition is to share the results of military-focused research in context with the broader auditory community.

Of the five human senses (hearing, smell, taste, touch, vision), hearing remains the sentinel sense in that it operates whether one is awake or sleeping. How many times have you awoken during the night because of a strange noise? Or perhaps a smaller number, how many times have you awoken because it was too quiet? An example of this detection function occurs within ships, where ventilation systems provide a background din, the absence of which is frequently an indication of an abnormal ship operation and cause for alarm. A second auditory function is to serve a location function: one hears a “click” sound which cues the vision system to look toward an estimated sector and then proceed with
high precision localization to “find” the rifle bolt closing of a sniper. A third auditory function is the identification of the type of sound (or the source of the sound) where the soldier in location example above may be able to identify the rifle type strictly by the sound heard without needing a visual cue. In layman terms, there is a significant acoustic difference between the sound of a city bus and a motor scooter; correct identification is an important distinction when crossing a street in terms of risk. More importantly, Service members communicate with each other primarily using their voice; hearing impairments affect performance in battle fields. Hearing and the subsequent auditory processing are critical for full human performance, and these four functions of hearing, in particular, are critical for military Service members.

One should consider that in today’s modern society, we live in an acoustically rich environment. In the daily pursuit of life, we are subjected to commuting noise (buses, trains, automobiles); electronic devices which provide distractions during transit times with music or podcasts; and the usual chores involving various mechanical devices such as lawnmowers, chainsaws, leaf-blowers, garden machinery and hair dryers. Many of us also find ourselves exposed to dangerous sound levels of 85 – 130 dB during our recreational activities like sporting events, both team and motor sports, as well as concerts. Part of the challenge we now face is the perception on how pervasive the noise threat is. There are business sectors who design sports venues to set noise records. A central United States sports arena recently boasted how the new facility set a new record as the loudest arena at 142.2 dB, beating the previous record of 136.6 dB. In this string of roar–of-the-crowd
record attempts, there are many more facility measurements greater than 120 dB. These levels rival sound pressures recorded on aircraft carrier flight decks, an environment known to produce hearing loss. Perhaps worse than the immediate danger presented in these cases is the damage done to public perception about the inherent risks associated with noise and the need to take action against those risks.

It is no small wonder that Center for Disease control (CDC) released a Vital Signs report (2017) which reports hearing loss is the third most common chronic health condition in the US. Almost twice as many people report hearing loss as diabetes or cancer. Military members are no exception. Military members, upon completing their service careers, have the option to enter the Veteran Administration (VA) system. The number of tinnitus and hearing loss cases awarded a Service-connected disability, according to the Veterans Benefits Administration, keeps increasing every year. The economic cost has been challenging to determine, but several estimations place it in the billions of dollars annually.
The military has unique challenges not found in industrial settings. Military acoustic environments can range from the quietness of an agrarian setting (30 dB) to an industrial setting of 90 to 118 dB in engine rooms or the roar of a flight deck/line at 150 dB (see Yankaskas et al. in this issue). First, many noise levels measured are beyond anything seen in industrial settings. Second, in these environments, military personnel are in close proximity and for long durations to the noise source, which can approach 24 hours a day, 7 days/week for prolonged periods of time. Third, mission takes priority over issues associated with proper use of personal protection equipment. Noise exposure can be acute, chronic or a combination thereof, and the resultant auditory injuries can be instantaneous or progressive. Due to such complexities, the assessment and prevention of auditory injuries in the military has been a challenge to accurately determine.
Summary of papers included in this special issue:

Due to the unique and highly complex environments, exposures, injuries, and requirements that US Service members are subject to, the Department of Defense Hearing Center of Excellence (HCE) and Office of Naval Research (ONR)’s Noise Induced Hearing Loss Program collaborated with a group of prominent scientists and distinguished leaders across many disciplines to bring you a 360-degree perspective through the collection of 23 articles that follows. The editors of this issue wish to tell the multi-layered story of military noise and the resultant hearing injuries which plague our Service members and Veterans and degrade their mission effectiveness and quality of life.

Impact of noise in the military (Issue I)

The first section in the issue attempts to set the scene for readers who may not be as familiar with military epidemiology, populations, environments, and functional requirements. As such, three epidemiology topics will orient the reader to the scope of hearing injury due to military service. Swan et al. discuss the prevalence of hearing loss and tinnitus specifically in Veterans who returned from combat in the Iraq and Afghanistan conflicts, while Nelson et al. will discuss the resulting disability awards the VA is responsible for when these Service members transition out of military service and into the VA healthcare system and Benefits Administration. Importantly, Nelson and colleagues conclude that participation in hearing conservation programs is associated with decreased rate of hearing loss disability awards after service, and thus present an evidence-base for consideration in increased hearing prevention efforts early on. The third epidemiology
paper, presenting early stage results, details the long-term outcomes of military noise exposure through a prospective, 20-year longitudinal study of Service members or recently separated Veterans.

Understanding the cause of these injuries is itself a complex undertaking. Rick Davis provides two short reviews about both long-term noise exposures and impulse noises, two of the most pervasive sound source signatures in military environments which often reach hazardous levels. Typical noise control hierarchy dictates first eliminating, quieting or otherwise controlling noise sources, followed by limiting exposures and protecting against them with the use of personal protective equipment (NIOSH, 2017). Yankaskas et al. discuss some of the successes with and remaining challenges to implementing these strategies in military environments. How to measure noise at all is its own challenge when space measurements do not adequately capture at-ear or in-ear noise exposures, as explored by Smalt et al., in the context of improving predictive models of actual auditory damage risk.

Issue I next explores the impact of hearing degradation on operational performance and the ways in which we can and seek to measure these effects. Keller et al. discuss reduced speech intelligibility in a Navy population, while Manning et al. and Le Prell et al. both offer insights into the demands and challenges of speech recognition in military communications. Finally, lasting difficulties with central processing of sound after blast exposure was explored in a prospective Veteran cohort by Bressler and colleagues, who note the importance of understanding confounding co-morbidities like PTSD in these
patients. Attempting to solve remaining mysteries of both peripheral and central auditory issues, Brungart et al. have developed a new Speech Reception in Noise (SPRINT) Test, shortened to 100 words in an attempt to more quickly distinguish “hearing impaired listeners with relatively poor speech intelligibility in noise from those with poor speech perception performance.” While the test offers improved time and comparably reliable data, the authors’ conclusions point toward still unmet needs for testing fitness-for-duty for future military standards.

Articles in Issue I should paint the picture of current problem the military faces in terms of scope of injuries, military-unique constraints to the typical hierarchy of noise controls utilized in non-military settings, current measures and the challenges which remain for adequately diagnosing and categorizing the status of Service members so we can best address prevention and treatment strategies, further explored in t Issue II.

**Biological mechanisms (Issue II)**

How to prevent NIHL relies on our understanding of the mechanisms of noise injury to both the periphery and central auditory pathways. In this issue, we start with a review on how our hearing system transmits sounds and how we assess noise damage. Paolis et al. summarize the analytical and numerical modeling of the hearing system from external ear to inner ear organ of Corti, hoping to simulate a variety of pathological conditions that lead to hearing loss.
We then follow with a general review on cellular mechanisms of noise-induced hearing loss by Kurabi et al. who summarize our current knowledge on the peripheral auditory sensory end organ, the cochlea, under various noise stimuli. The authors highlight the intracellular stress pathways leading to apoptotic and necrotic cell death upon noise injury. The molecules in such pathways could serve as potential therapeutic targets for interventions against NIHL.

Recently the topic of “hidden hearing loss” with cochlear synaptopathy has become prominent. This phenomenon depicts the transient damage of suprathreshold noise to the afferent synapses but long-term degeneration of low spontaneous rate fibers that are not easily detectable in normal auditory tests (i.e., ABR and DPOAE). Here we include four papers on this topic. Kujawa and Liberman, who originally discovered such phenomena, describe their perspectives on the phenotypes and mechanisms. So do Kobel et al., who provide their own unique perspective on this topic. Lobarinas et al. further present their findings on correlations between suprathreshold noise-induced synaptopathy and ABR amplitudes as well as transient threshold shift (TTS) in animal models. Finally, Hickox et al address how to translate parameters discovered in preclinical models to clinical populations with hidden hearing loss, a major challenge for translational therapeutics for hearing loss.

Addressing stymied efforts to develop therapeutics for NIHL, Hammill describes her perspective on FDA drug approval processes and how understanding these intricate processes benefits drug development for hearing loss. Whilton further describes her
attempt to screen and identify effective drug candidates for spiral ganglia upon noise injury. Finally, Zheng and Zuo describe their perspective on regenerative approaches to hearing loss and drug development, focusing on hair cell regeneration and its similarity to normal hair cell development.

The central auditory pathway plays a critical role in tinnitus (ringing in the ears), a significant outcome of military noise that affects our military Service members and veterans. Two papers review recent findings on auditory thalamic circuits and other brain regions and their implications in tinnitus. Caspary and Llano summarize the recent advances in inhibitory neurotransmitter systems (i.e., GABAA receptor) in auditory thalamus and their relationship to noise-induced tinnitus. Chen et al. describe their findings on salicylate-induced tinnitus and hyperacusis animal models where they discovered enhanced responses in several brain regions (caudal pontine reticular nucleus and cerebellar paraflocculus). These studies provide strong evidence for mechanisms of tinnitus involving neural amplification in central auditory pathway and other brain regions linked to arousal, emotion, and motor control.

Perspectives

In addition to these articles included in this Special Issue, the editors realize that we have not discussed many other important subjects related to noise in the military. Of particular interest is the use of hearing protection devices (HPDs). Despite the shortfalls in correct daily usage of HPDs among military personnel, significant advances have been made recently in developing advanced HPDs. Moreover, genetic predisposition to noise-
induced hearing loss has been studied among a subset of Marine Recruit study population who sustained hearing loss during rifle training compared to those who maintained their hearing. Such populations provide a unique resources to identify genetic factors and therapeutics that might help elucidate roles of oxidative stress and inflammation in NIHL.

The editors hope that this collection of work will illuminate the unique challenges posed to the military operational leadership, the public health and surveillance communities, the DoD and VA healthcare systems, and the Service member and Veterans themselves. There are many remaining knowledge gaps to fill and this collection should highlight the most persistent and important issues to tackle across the various disciplines involved.
5.3.2 A review of the progress and pitfalls of FDA policy process: Planning a pathway for pharmaceutical interventions for hearing loss development


URL: http://dx.doi.org/10.1016/j.heares.2016.11.006

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Abstract

The Federal Food and Drug Administration, or FDA is generally considered a powerful gatekeeper, able to deliver or withhold life-saving cures and create or destroy economic windfalls. As the decades go by, and technologies, diseases, public health demands, and politics evolve, we can identify patterns of change, action and inter-action among some of these traditional stakeholders in the FDA’s policy sphere. A careful examination of this agency’s colorful history can shed light on central features of the agency’s policy process, which has been quite receptive to its stakeholders and adaptive to change over the decades and, in turn, show the way for development in lanes which do not fit neatly into the current paradigms offered by the agency. This paper will explore the history of FDA policy process, through examination of seminal moments in FDA history, the prominent actors and focusing events within them, and the outcomes of those events, in an attempt to illuminate a pattern of behavior or processes by which a struggling field of pharmaceutical development such as interventions for hearing loss can advance.
Introduction

The Federal agency known as the Food and Drug Administration, or FDA, is many things to many people. To the American public, it has traditionally been revered as a protector of public health and noble opponent to potentially harmful quack medicine. To the pharmaceutical, medical device and biologics industries, it has generally been considered a powerful gatekeeper, able to create or destroy economic windfalls. To the higher echelons of American political actors, including Congress and the President, the FDA is often used as a political mechanism of action. As the decades go by, and technologies, diseases, public health demands, and politics evolve, we can identify patterns of change, action and inter-action among some of these traditional stakeholders in the FDA’s policy sphere. A public which is increasingly skeptical of all government agencies begins to seriously entertain criticisms of the once-beloved agency (Zelizer, 2012); an industry that is increasingly compartmentalized into niche areas of concern and lifecycles shows equivalently increasing frustration with the heavy burdens of FDA bureaucracy; Congress flips from criticisms of FDA granting approvals too quickly, to lashing criticisms of delays in approval rates; and policies created to protect and inspire innovation become a hotbed of criticism for stymying development of technologies intended to treat the poor and indigent. The constant in the turmoil is the web of complexity by which the FDA operates internally and in collaboration with related Federal agencies, including the National Institutes of Health (NIH), the Department of Defense (DoD), National Trade Commission (NTC), the Department of Health and Human Services (DHHS), the Public Health Service (PHS) and its subsidiaries like the Center for Disease Control (CDC), among others. The entirety of the FDA universe in all its history, controversy and seemingly limitless power has created a shroud of mysticism and bafflement through which its
primary customers – the patients, medical community, and technology sponsors – must learn to see through in order to successfully interact with the agency.

A careful examination of this agency’s colorful history, however, can easily dissolve that shroud and shed light on central features of the agency’s policy process, which has, in reality, been quite receptive to its stakeholders and adaptive to change over the decades. Such an understanding of the workings of the FDA can in turn show the way for development in lanes which do not fit neatly into the current paradigms offered by the agency. The purpose of this paper is to attempt just that: to explore the history of FDA policy process, through examination of seminal moments in FDA history, the prominent actors and focusing events within them, and the outcomes of those events, in an attempt to illuminate a pattern of behavior or processes by which a struggling field of pharmaceutical development can advance. In his article which attempts to “attempt to identify and analyze the major historical changes and influences that have shaped the regulation of biotechnology by FDA,” David L. Stepp argues that one can predict the future of FDA policy changes if equipped with, “a knowledge of the standard ways in which FDA policy has evolved historically, the pressures and influences that prompted those historical changes, and an appreciation of the influences that exist currently and their likely effect” (Stepp, 1999). In a similar fashion, this paper will use examples from past and present dealings with the FDA, in a novel attempt to show how a struggling field of FDA-regulated development can craft its own pathway through and with the seemingly “Wizard of Oz”-like agency. Specifically, this paper will attempt to demonstrate the actual flexibility of the FDA, and, firm in that perspective, to carve out a feasible pathway for developers and stakeholders in pharmaceutical interventions for hearing loss, in particular, to navigate toward an approved drug or set of drugs in a coordinated effort with the FDA and other invested Federal agencies.
FDA History: a review from a policy process perspective

Like most Federal agencies, the FDA is a heavily loaded bureaucracy which sits under the Department of Health and Human Services; but unlike most Federal agencies, the FDA is responsible for one of the most highly regulated industries in the United States, the pharmaceutical industry (Carpenter, 2004). Additionally, it is responsible for the regulation of foods; medical devices; radiation-emitting products; vaccines, blood and biologics; cosmetics; and tobacco products (FDA, 2015). The standard product oversight categories for medical development encompass many subsets and, conversely, also manage to regulate supra-categories like biotechnologies which “do not comprise a distinct product group within FDA, but are instead categorized on a product-by-product basis as a “food”, “drug”, “device”, or “biologic” (Stepp, 1999). In order to properly frame the conversation at hand, and create a sense of understanding of this massive bureaucratic body, it is important to begin with a brief understanding of the timeline of development and evolution of the FDA.

The FDA’s timeline functionally begins with the Pure Food and Drugs Act of 1906. With that Act, Congress first granted FDA significant authority to regulate drugs with civil and criminal penalties, prohibiting “interstate commerce in “adulterated” or “misbranded” drugs” (Stepp, 1999). Under the 1906 Act, a drug was recognized as such if it was “recognized by the United States Pharmacopoeia or National Formulary for internal or external uses...[or] intended to be used for the cure, mitigation, or prevention of disease in either man or other animals” (Stepp, 1999). However, in 1911, the Supreme Court of the United States “substantially limited the scope of the 1906 act by interpreting the definition of “misbranded” to prohibit only claims that were false or misleading as they related to the identity or ingredients of the drug mixture, but not to prohibit false or misleading claims regarding the therapeutic effects of a drug” (Stepp, 1999). This distinction
would drastically limit the authority and scope of the early FDA, as congressionally enacted into
the Amendment of 1912, or the Sherley Amendment, for the next 25 years. Notably, it would also
be the last major decision in the courts ruled that was not in favor of the FDA.

In 1937, the poisoning deaths of over 70 people caused by an elixir called Sulfanilamide
proved the inability of the FDA to protect the public under the constrained authorities provided by
the 1906 Act and Sherley Amendments (Stepp, 1999). Basic scientific tests could have prevented
the elixir from being released into the public, but the FDA’s only authority was to restrict the
branding as an “elixir”, technically defined as an alcohol-based solvent, which Sulfanilamide was
not (Stepp, 1999). As a direct result of this focusing event, Congress enacting the Federal Food,
Drug and Cosmetics (FDCA) Act of 1938, otherwise known as “the 1938 Act”, which is still the
foundation of FDA authority today.

The 1938 Act provided the FDA with “authority for premarketing review of drugs” which
set up both new Investigational New Drug (IND) and New Drug Application (NDA) systems.
Further, although the FDA had been petitioning Congress for the ability to expand its authority
over advertising allowed by manufactures, Congress instead gave that authority to another Federal
agency, the Federal Trade Commission (FTC). In response, the FDA greatly expanded its own
definition of “mislabeled” to compensate for its lack of inherent authority on the branding and
labeling of drug products (Coleman, 2014). The FDA’s new strict “definition of “mislabeled”
reflected both changes in the state of medical evidence and in the views of courts[, who upheld the
interpretation,] toward FDA’s exercise of misbranding jurisdiction. This new definition also solved
the problems created by the Sherley Amendment by no longer requiring FDA to present evidence
concerning the intent or state of mind of the manufacturer; FDA needed only demonstrate that the
product did not meet the claims of its labeling” (Stepp, 1999). Further, the 1938 Act added FDA
authority to inspect manufacturing facilities, [and] creat[ed] an easier pathway to criminal convictions of corporate officers (Stepp, 1999). However, the FDA was still, by the authority vested in the 1938 Act, limited to concerns of safety, and only that of new drugs, and had no control over claims of actual efficacy. All a manufacturer had to do was claim their products were “generally recognized as safe” to keep the FDA off their back, as the FDA held the burden of proving otherwise. Many generic drugs were able to hit the market, claiming other previous NDAs of the “pioneer” drug formula showed that their product, too, was then “generally recognized as safe” (Stepp, 1999). This apparent void of FDA authority did not last long in keeping the FDA out of efficacy concerns, however. Instead of staying away from the issue, the “FDA took the position that the concept of drug safety can be viewed as a risk-benefit calculus, and, therefore, some consideration of efficacy—the benefit in the calculus—is inherent in the determination of safety” (Stepp, 1999). This becomes the first of many examples where the FDA’s administrative practices reflected its believed mission whether in the absence or presence of actual regulatory authority to act, and in such a manner, actually predicted its future legislative and regulatory state; a sort of “manifest destiny” of the FDA, if you will.

Despite the lack of actual authorities granted to monitor product efficacy, the FDA was running fairly smoothly with its creative definition strategy, coupled with a strategy to self-institute “a prescription-only drug system,…although it had no apparent statutory authority for such a system. [However,]…in 1951 Congress codified that system in the FDCA”, showing further support for, and essentially the codification of, the FDA’s mission to protect the public (Coleman, 2014). These parallel strategies afforded the FDA an understood authority, if not a clearly defined one, to deter any release of products not specifically approved for specifically intended purposes. This situation would change in 1957 when the drug Thalidomide was widely prescribed to pregnant
women across Europe as a sedative, resulting in an epidemic of birth defects known as “phocomelia” which often manifested as missing or malformed limbs in the surviving children. While it was never released in the U.S., the harmful effects were already known through a U.S. FDA trial. Without broader formal FDA authority, however, the product was released in Europe anyway (Stepp, 1999). This event focused attention on the authority deficit and led directly, if not swiftly, to “the Drug Amendments of 1962” or Kefauver-Harris Amendments (Orlando, 1999).

Commonly referred to as “The Amendments,” this new set of rules expanded FDA authority via expanded scope of interstate commerce regulations, forbidding interstate commerce of any new drug that was not the subject of an NDA approved by and not merely in pursuit with FDA, or without the FDA’s approval of the IND, not just IND filing, “thereby transforming the role of FDA from policeman to gatekeeper” by prohibiting the cross-stateline shipment of investigational drugs without the FDA’s approval (Stepp, 1999). These regulations also explicitly addressed expanded authority to review and approve efficacy merits on an indication-for-use basis, deciding that “each different therapeutic use of a product requires individual approval under the 1962 Amendments” thus creating a new “Supplemental NDA” for sponsors to apply for approval of new indications of already approved drugs, as well as newfound “control over the design and implementation of the clinical trial process” (Stepp, 1999). Thus was born the modern clinical trial process which the FDA had been struggling to impose through its previous creative uses of definitions and scope creep.

This new authority was retroactively applied to pre-1962 drug approvals as well, a process in which drug sponsors would have the right to a hearing to defend their products against a ban. This created an obvious administrative burden the FDA would never be able to keep up with, so they again employed some creative definitions, this time for acceptable data collection and clinical
trial design requirements. Essentially, the FDA required current-day, rigorous standards, which they had just created, be applied to any trials which produced submitted evidence of safety or efficacy. Thus any pre-1962 manufacturer would surely fail to live up to these standards and have no case for approval without starting from scratch to build sufficient clinical evidence of efficacy/safety data. The Supreme Court of the United States (SCOTUS) upheld this redefining tactic, demonstrating again a pivotal and supportive stance of the courts on behalf of the FDA (Stepp, 1999). Coleman reflected that the “Supreme Court decisions that upheld FDA’s position but, by using the abstract language loosely, permitted an interpretation that the decisions had gone far beyond what the FDA had argued, [so that t]welve years later,…FDA concluded that, although it had asked the Court for a little, it had been given a lot” (Coleman, 2014).

Generics, too, were affected by these provisions, as their previous designation of “generally considered safe” clause was never approved or disapproved but instead now became dependent upon the pioneer NDA for approval, so that if a pre-1962 pioneer NDA became disapproved, so too did all dependent generic applications, which was again upheld by the SCOTUS, proving itself once again to be a pivotal actor in the successful authority expansion of the FDA and focusing of its mission of public health protection activities, as broadly defined as required (Stepp, 1999).

Further regulations passed in the 1960’s expanded the role of manufacturing oversight, leading to the current Good Manufacturing Practices (GMPs) in use today. These affect labeling, manufacturing plant standards, packaging and more, all required to have FDA approval and subject to inspection and seizure. All of these new regulations greatly reduced the speed at which a drug could secure an approval for release for public marketing. It wasn’t until the 1980’s when the delayed approval process had hit its peak of durations, coupled with other focusing events, that speed of approvals became a major political force which shifted the regulatory trend hitherto of
increased scrutiny and expanded oversight, toward decreased approval times and streamlined regulatory processes. Manufacturers began to heavily pressure Congress to speed approval processes and President Ronald Reagan issued an executive order for “all Federal administrative agencies to assess their existing regulatory frameworks and to suggest potential reforms” which established the “Task Force” on Regulatory Relief, chaired by Vice President George H.W. Bush. Mr. Bush identified FDA approval processes among the top 20 reform-ready programs (Stepp, 1999). Thus, DHHS pledged to reform both the FDA IND and NDA programs, and did so by 1982, again in 1987 and yet again in 1988 after V.P. Bush again led a task force to expedite treatment in life-threatening circumstances (Stepp, 1999).

The AIDS epidemic was a focusing event for many areas of Public Health and science in general during the 80’s, but for the FDA, it was directly responsible for the creation of new expedited review and approval pathways, though resulting provisions were more broadly defined to include both life-threatening and severely-debilitating diseases such as “diseases or conditions that cause major irreversible morbidity (e.g., blindness or neurological degeneration)”, “Expanded Availability”, “Surrogate Endpoint” and “Parallel Track” investigations were all creatively drafted into new regulatory pathway options by 1992 to ensure greatest expediency and broadest access to experimental agents for terminal patients (Stepp, 1999). These were all processes the FDA had administratively approved in the early days of the 80’s AIDS epidemic despite lagging regulatory formalization well into the 90’s (Stepp, 1999). The FDA had not been waiting until formal authority or codified processes were passed to respond to the pressing political and public needs.

Another example of this propensity to act and then revise or update as needed is found in the device regulation side of FDA. The Medical Device Amendments (1976) to the 1938 Act were not written with allograft heart valve tissue in mind as that substance would not be invented for
many years to come. However, the FDA had already “involved itself in the tissue banking community for many years …limited to…monitoring the activities of tissue banking, and engaging in dialogue with the tissue banking community. This passive role changed when the FDA’s Center for Devices and Radiological Health (CDRH), announced a meeting to be held in June, 1990” wherein the FDA presented “requirements for the types of data to be submitted for premarket approval for mechanical or biological heart valves introduced into interstate commerce after the enactment of the 1976 Medical Device Amendments to the Food, Drug and Cosmetic Act,” thereby creating the standard that henceforth, the FDA would be regulating heart valve allografts as Class III Devices, the most strictly regulated of the 3 classes of medical devices (Bottenfield and Deuel, 2005). This prompted a consortium of industry representatives to file suit against the FDA, which again was dismissed by the FDA-friendly courts.

A few remaining evolutions of FDA approval regulations and processes warrant mention in this context; all are attempts to meet a need un- or underserved by existing FDA policies. The first is the emergence of Orphan Drug classifications. Two Acts in the early 80’s created a frenzy of drug approvals. The first, known as the Bayh-Dole Act of 1980, “beloved by the biotechnology and investment communities” allowed scientists, universities, and small businesses to patent and profit from discoveries they made through federally funded research which they had not previously been able to do. This resulted in an increase in patents from 380 in 1980 to 3,088 in 2009” (Markel, 2013). In the second pivotal piece of patent-related legislation, known as “The Drug Price Competition and Patent Restoration Act of 1984” or Hatch-Waxman Act, Congress created extensions to innovator drug patent terms and provided “provisions for the marketing of generic versions of patented drugs on the day after patent expiration” and “opportunities to challenge the validity of patents issued to innovator drug companies,” thus creating a boon for generic
development simply by clarifying the previously murky pathway (Melethil, 2005). Fast forward to
the new millennium, and the slowing pace of pharmaceutical innovation as evidence by lower rates
of first-in-class and “blockbuster drug” approvals and growing patent expirations from those early
filers in the 80’s and 90’s, and one can understand the need for the pharma industry to redesign
itself away from blockbusters, toward “niche busters” also known as Orphan Drugs (Sharma et al.,
2010). The Orphan Drug Act of 1983 was intended to create incentive and pathways toward
development of technologies to treat rare conditions as defined by low numbers of incident cases
in the public. The Act has also been interpreted to cover “drugs that are not developed by the
pharmaceutical industry for economic reasons but which respond to public health need” (Sharma
et al., 2010). The latter assignment of orphan status for economic reasons rather than quantitative
rarity of condition to treat is a matter of public policy and politics and, as such, is highly subjective
an rarely used.

Devised in the 90’s, “Neglected Diseases” programs for tropical diseases typically
impacted the impoverished nations south of the equator (Trouiller et al., 2002), and “Accelerated
Approval” programs for expedited approval pathways for terminal conditions, have all been
developed in a similar fashion as Orphan Drug programs (Dagher et al., 2004; Orlando, 1999).
They have a targeted gap in broader FDA policy to fill, all with interdisciplinary collaborations
with other Federal agencies (e.g., NIH and CDC most often), and with a mission to innovate safe
and efficacious therapies to populations in need. Continuing this trend toward expedited fast-tracks,
2013 saw the creation of a program for “Breakthrough Drugs” to spur continued focus on
innovative new therapies in general, which has seen a robust response from industry with more
than 200 requests for “breakthrough” designation to date (Wechsler, 2015). How these programs
will evolve and impact drug development remains to be seen, but the point has clearly been made
that the FDA is willing to move beyond current policy confines in directions that “make sense” to meet new challenges as the evolving world of medicine and disease warrant.

**How the Department of Defense (DoD) Interacts with FDA**

The DoD has always had to meet the unique medical needs of a battle-field-exposed service member population. Those requirements vary from extreme battlefield trauma, to occupational hazard exposures above and beyond limitations imposed on civilian workforces by Federal agencies (e.g., Occupational Safety and Health Administration, or “OSHA”), to chemical or biological warfare (CBW) exposures. The first and second of these have garnered much intramural as well as public-private partnership research focused on general improvements in emergency medical care or personal protective equipment (PPE) and generally follow traditional FDA pathways as they have evolved, to include “Emergency use” designations granted by the FDA for some exciting breakthroughs in areas like limb replacement and hemorrhage treatments. However, the CBW category has demanded new and innovative ways of working with the FDA to meet DoD requirements.

The DoD had $6.5 Billion in drug expenditures (a small fraction of all U.S. human-use drug sales) during the 2007 fiscal year, and provided care through its benefits program, TRICARE, to 9.2 Million active duty, retired military personnel and their dependents (Trice et al., 2009). While the DoD is a purchaser of most DoD formulary drugs commercially, it can and does serve a role as developer of drugs and biologics (primarily vaccines) (Rettig, Brower and Yaniv, 2007). Indeed, since 9-11 and resulting heightened war activities, the DoD has increasingly served as both the developer and sole purchaser (and thus sole market) of vaccines needed to thwart the likes of anthrax and other malicious CBW threats to national security. As the developer, the DoD is
involved in the full spectrum of research activities and thus responsible to the FDA for all aspects of regulatory compliance, to include human clinical trials. However, it is obviously unethical to test known harmful agents on human populations, so the DoD worked closely with the FDA to create the 2002 “Two Animal Rule” whereby safety data in humans, combined with efficacy data in at least 2 animal models, could be submitted for market approval of a drug or biologic (Rettig, et al., 2007; Martinez, 2007; Gronvall et al., 2007).

However, outside of the CBW class, few drugs and biologics developed by the DoD ever “move beyond the IND stage, largely because few economic incentives exist for pharmaceutical firms to develop military use–only products and because of the difficulty of generating data on efficacy” in an operational environment (Rettig et al., 2007). Couple that with a well-documented understanding that the DoD is ill-equipped to handle drug development due to, among other cited reasons, a lack of centralized oversight, lack of mission focus or experience in clinical research, and, perhaps most detrimental, a “highly fragmented organizational structure” (Martinez, 2007). This has led to chasms between developmental pathway stages, between basic science and product development, which leave technologies languishing in the “valley of death” of the advanced development/clinical trials stage (Martinez, 2007; Gottron, 2010). To address that valley in CBW research, the then President of the United States, George W. Bush proposed project BioShield in 2003 and it was enacted in 2004 to ease the regulatory way for approval of successful treatments and prophylactic agents as well as create guaranteed government purchases in the billions of dollars (Gottron, 2010). The market guarantee element was unprecedented in drug development, and drew sharp criticism for the potential wasted money, but it did successfully generate public and private research interest in an otherwise unattractive market. Nonetheless, Congressional scrutiny of BioShield, including its large leap from basic research to production (failing to address the need
for mid-level/Advanced Development stages of research), and coupled with a Democratically controlled Congress pitted against a Republican President, led to creating the Biodefense Advanced Research and Development Authority (BARDA) in DHHS through the Pandemic and All-Hazards Preparedness Act (P.L. 109-417), as “a dedicated infrastructure to manage and fund advanced development and commercialization of CBRN countermeasures.” While stopping short of canceling BioShield, Congress continued to fund BARDA through 20134 with sizable transfers from BioShield accounts (Gottron, 2010). The intent of BARDA, like BioShield, was to take these specialty market requirements from IND to NDA successfully and timely. For lack of time here, I cannot go into the many reasons why these programs, perhaps not surprisingly, disappointed with meager product approvals to show for the billions invested in this partisan battle.

**Hearing Loss in the DOD Population and FDA Pipeline**

Hearing loss affects millions of active duty Service members and Veterans and is the most prevalent and expensive disability affecting Veterans as a direct result of service, according to every annual Veteran’s Benefits Administration Annual Report for decades (VBA, 2014). Billions are spent annually in these disability costs alone, compounded by healthcare costs, quality of life degradation and any costs directly or indirectly assumed by the DoD. Yet there are very few clinical research studies completed to date examining safety or efficacy of a pharmaceutical intervention for the prevention or treatment of hearing loss. As the chair of a DoD working group on the subject, I can report that there are in fact less than half a dozen and none of them are close to applying for their NDA.

Pharmaceutical interventions for preventing or treating hearing loss have stalled for over 40 years since mechanisms of injury and proposed compounds were first identified to attack those
mechanisms, even though there are now dozens of such compounds waiting on the doorstep of clinical trials. The problem can be boiled down to the same conundrum CBW trials faced – it is unethical to expose human beings to a harmful event in the name of research. Noise-induced hearing loss is largely preventable with proper PPE, so scientists cannot easily design an ethical clinical trial wherein subjects are not intentionally exposed to hazardous noise without proper protection. Military environments routinely expose Service members to hazardous noise, but data limitations have prevented proper identification of ideal clinical trial subject pools to date. If the DoD were able to properly identify injured populations, it would have a moral imperative to immediately improve hearing conservation and prevention efforts to protect them, and the scientist would go back to the drawing board.

**Conclusions**

A precedent exists, set recently and much more dramatically seen in the CBW vaccine developments, of creative and collaborative work between the FDA and the DoD to achieve necessary requirements together. Further, there is precedent in the FDA for maintaining a high level of flexibility and dedication to filling under-served populations. As exemplified in the recent convergence and policy action points of 1) political (Congressional and Presidential engagement), 2) policy (of the FDA and similar international regulatory bodies) and 3) problem (under-served poverty markets, niche/orphan populations or emergent threat response requirements) streams, opportunities to create specialized categorical development pathways can be created and seized (Kingdon, 2011). The currently stymied field of hearing loss pharmaceuticals could follow suit by creating its own metaphorical “wave of opportunity” in which to push forward (Kingdon, 2004).
Primary actors in FDA policy process include other Federal agencies like the DoD and the Congressional and Presidential actors who are generally very supportive of DoD troop health issues. The courts have been historically friendly toward FDA prudence of regulatory authority and interpretative policies when public welfare is at the heart of the matter, and industry would benefit from development in this area with potentially one of the largest markets in pharmaceutical history laying in the balance (Coleman, 2014).

The fact remains that the FDA has demonstrated itself to be highly influenced by its stakeholders – from patient advocacy groups, the medical community, other Federal agencies, U.S. leadership, and industry – and all of these groups have a converging interest in preventing or curing hearing loss. There has to be a policy entrepreneur to bring these positions together; a “mobilization of drug-specific lobbies—the firms and the patients” (Carpenter, 2004). I posit that none could be more appropriate or better poised to serve that function than the DoD itself with an economic interest, moral imperative to its troops, history of regulatory creativity and collaboration with the FDA, mandate to serve as both producer and purchaser if need be, and the political clout to force the conversation. “FDA drug review is an exercise in learning shaped by organized interests” and the FDA remains highly responsive to “opinion leaders” (Carpenter, 2004). Further, the FDA “has been punctuated by periods of growth and retrenchment as the political climate for regulation has responded to events, interest groups, and ideology” (Eisenberg, 2007). The hearing loss research interest groups stand at a pivotal juncture where the possibility of a successful development pathway is only an organized response to the FDA away.
The third production of special collection papers was selected for submission to the International Journal of Audiology. This collection delves into the next frontiers of the PIHL group, as described in Chapter 4 above. Focused on Clinical Monitoring for Ototoxicity, the articles in this collection use the same first step as the noise-focused grouping did in the Otology & Neurotology collection: namely, a literature review-to-BRP model. This “low-hanging fruit” of existing evidence-based and expert consensus-based development of best practices in clinical research resulted in eleven manuscript submissions. The two co-authored contributions included herein focus attention on non-pharmaceutical Ototoxins, many of which may be encountered in noisy environments which can result in summative or synergistically higher injury rates (Hammill et al., in review), and a review of PIHL agents currently under investigation for protection from ototoxicity (Hammill & Campbell, in review).
5.4.1 Non-Pharmaceutical Ototoxins: A Review for Hearing Healthcare Stakeholders

Hammill, Tanisha L.; McKenna, Elizabeth; Hecht, Quintin; Buchanan, Kari; Pryor, Nina.

Abstract:
Objective: This review will summarize information from the overall body of published literature regarding ototoxic chemicals encountered outside of clinical exposures, largely in occupational settings. While summarizing the most common non-pharmaceutical ototoxins, this review will provide clinically relevant information and recommendations such that hearing health professionals may adopt a more comprehensive and appropriate diagnostic case history, test battery, documentation scheme, and education delivery.
Design: Solvents, metals and asphyxiants literature was non-systematically reviewed using PubMed, national and international agency websites, and communications with known ototoxicity experts.
Results: Initial intentions to summarize existing programs for occupational ototoxicity monitoring fell short when it was discovered that such programs have not yet formalized across the major oversight agencies in the United States. Instead, recommended guidance
documents and fact sheets, which highlight existing occupational exposure limits and suggest monitoring and education are discussed.

Conclusions: While evidence in humans is limited, potentially ototoxic substances are worthy of improved surveillance and further research to understand their ototoxic mechanisms, effects, and possible mitigation strategies. A triad approach of monitoring, protecting, and educating is recommended for effective prevention of hearing loss: the Department of Defense (DoD) Hearing Center of Excellence (HCE)’s Comprehensive Hearing Health Program (CHHP) model employs such an approach.

Introduction

Within audiology literature, it is well-cited that over 22 million workers in the United States (US) are employed in hazardous noise environments (NIOSH, 2016) and that 10 million Americans are estimated to suffer from noise-induced hearing loss (NIDCD, 1999). While the connection between noise and hearing loss is understood, and (as discussed elsewhere in this supplemental edition) the correlation between certain classes of pharmaceutical medications and their ototoxic consequences are well-documented in the literature, the same cannot be said for non-pharmaceutical chemical exposures and hearing injury. Only since the late 1970s have investigators evaluated potential occupational chemical ototoxins. Four decades later, evidence which establishes a clear causal pathway from chemicals – such as organic solvents, metals, asphyxiants, and pesticides – to hearing loss is relatively scarce. The growing body of animal research in ototoxicity has demonstrated mechanisms of action and audiometric consequences, while similar
outcomes and risks, respectively, have been noted in correlative human observational and epidemiological studies (Vyskocil, 2012). Given the increasing evidence that humans exposed to organic solvents, metals, asphyxiants, and pesticides may experience significant auditory dysfunction, the need for better understanding of these ototoxins, specific damage risk criteria for ototoxin exposures, as well as preventive measures, is evident.

In the U.S., the Occupational Safety and Health Administration (OSHA) is the regulatory lead for workplace safety and establishes permissible exposure limits (PELs) for chemical and physical hazards in the workplace. OSHA works closely with the National Institute for Occupational Safety and Health (NIOSH) which researches, develops, and recommends best practices in occupational health and prevention, including worker protection from potentially hazardous chemical substances. Since 1996, NIOSH has been involved with the National Occupational Research Agenda (NORA), a collaborative program with international partnerships to direct and grow research toward the improvement of workplace practices and safety (NIOSH, 2016). One of the ten NIOSH sector programs includes “Preventing Hearing Loss from Chemical and Noise Exposures” as a focus area (NIOSH, 2016). Outcomes from this program include an extensive review of noise and industrial chemicals and their effects on hearing and balance (Prasher et al, 2004) as well as the first detailed criteria of ototoxic risks from occupational chemical exposures (Johnson & Morata, 2010). While these documents remain the most comprehensive and seminal pieces of literature on the topic to date, the current review will summarize information gleaned from them as well as original published research. While
focusing on the most common non-pharmaceutical ototoxins, this review will summarize evidence from human studies and provide clinically relevant information such that hearing healthcare providers may adopt a more comprehensive and appropriate diagnostic case history, clinical or monitoring testing battery, and education delivery. Additionally, the authors hope to encourage industrial hygienists and safety professionals to increase hazard control, monitoring, and documentation of both noise and ototoxin exposures.

**Organic Solvents**

A solvent is a chemical that can dissolve other substances, and is used widely in manufacturing, dry cleaning, painting, and varnishing. Solvents can be inhaled or absorbed through the skin and the toxicity is neurotoxic in nature. Although not all solvents are ototoxic, chemicals with sufficient evidence of ototoxicity from human studies include toluene, xylene, styrene, and mixtures of these organic solvents. The following reviews the human evidence for organic solvent ototoxicity; for a comprehensive summary of human and animal studies, see Vyskocil et al (2012), Johnson & Morata (2010), and Gagnaire & Langlais (2005). Additionally, sufficient animal studies support n-hexane, trichloroethylene and ethyl benzene as likely ototoxic in humans.

The damage from ototoxic solvents is largely to the central auditory nervous system (Johnson, 2010) as neurotoxic agents; however, Hsu et al (2015) reported that damage can be observed “from the utricle to the saccule, cochlea and semicircular canals.” Exposure to organic solvent mixtures has also demonstrated vestibular dysfunction in limited human
studies. Abnormalities in the ocular vestibular-evoked myogenic potentials (oVEMP), cervical VEMP (cVEMP), and caloric tests were noted in patients who had long-term (21 years +/- 4 years) exposure to organic solvents, and subsequently experienced symptoms of inner ear and vestibular dysfunction. It may be important to note that the individuals studied in Hsu et al (2015) had work environments with noise levels <90 dBA. Some organic solvents can interact with noise exposure in an occupational setting, resulting in a synergistic effect on the auditory system in which more damage is found than expected in comparison to solvent or noise exposures in isolation; this interaction is discussed below based on several human studies.

*Toluene*

Toluene is a water-insoluble compound often used in paint thinners, cleaners, and adhesives. The primary method of absorption is inhalation. The ototoxicity of toluene has been researched in animals and humans, and found to affect the central auditory pathway, similar to other solvents that can produce neurologic dysfunction. In humans, evidence of retrocochlear involvement has been noted in auditory brainstem responses (ABR). Wave latencies, both absolute for wave I and interpeak latencies for waves III-V, were prolonged and decreased amplitudes were noted in printing plant workers exposed to low concentrations of toluene long-term compared to non-neurotoxic agent exposed workers, even when factors such as hearing status, medical and lifestyle history were considered (Vrca et al, 1996).

*Ethyl Benzene*
Ethyl benzene is a clear, liquid compound used in the production of fuels, paints, and plastics with an odor similar to gasoline; the occupational exposure is typically inhalation. A common non-occupational exposure of ethyl benzene is cigarette smoke. No human studies are available on this compound; however, evidence in animal studies supports mid-frequency cochlear damage and potential interaction with concurrent noise exposure (Vyskocil, 2010).

**Xylene**

Xylene is a highly flammable solvent that is often used as a cleaning agent, in paints, paint thinners, plastics, pesticides, and in medical laboratories. It has three isomers (ortho-, meta-, and para-xylene), annotated as o-xylene, m-xylene and p-xylene, and is usually absorbed through inhalation. Fuente et al (2013) conducted a human study in which xylene-exposed laboratory workers were compared to non-exposed university employees by examining pure-tone thresholds, distortion-product otoacoustic emissions (DPOAE), ABR, and behavioral auditory processing disorder (APD) tests. Air samples were obtained and analyzed to determine exposure levels to xylene, and urine specimens were collected and analyzed for a metabolite of xylene, methyl hippuric acid. None of the occupational exposure limits (OELs) for xylene were exceeded in the exposed group, and none of the study participants reported hazardous occupational noise exposure. The subjects exposed to the highest concentration of xylene showed significantly worse pure-tone thresholds compared to non-exposed peers. Conversely, no significant differences in DPOAEs were found between the two groups, however, abnormal ABR results were characterized by
wave V latency and I-V interpeak latencies that were significantly greater in the exposed than the non-exposed group. Despite differences in ABR test results, no dose-dependent relationship was found. Xylene-exposed workers presented poorer results compared to the non-exposed peer group in central auditory tests, specifically the Pitch Pattern Sequence (PPS), Dichotic Digits (DD), and the Hearing in Noise Test (HINT) composite. No significant differences were noted on the Masking Level Difference (MLD) test, the Adaptive Tests of Temporal Resolution (ATTR) or a Speech Reception Threshold (SRT) obtained using HINT sentences. There were no significant correlations between xylene-concentration by biomarkers in the urine samples and the APD test results. The authors suggested xylene exposure may affect central auditory nervous system functions, particularly temporal ordering, binaural integration and speech perception in noise, and suggested monitoring protocols for workers occupationally exposed to xylene beyond pure-tone audiometric monitoring; specifically, ABR, PPS, and DD may inform clinicians on the hearing health of workers exposed to xylene occupationally (Fuente et al, 2013).

The ototoxicity of xylene and p-xylene has been researched in animals and humans, although the effects of concurrent noise exposure have not been proven (Johnson, 2010).

Styrene

Styrene is commonly used in the manufacturing or processing of polymers (plastics), and the absorption pathway is largely inhalation. A human study by Triebig et al (2009) investigated laminators from a boat building plant who were exposed to styrene. The workers were evaluated using pure tone audiometry through 16,000 Hz and transient
evoked otoacoustic emissions (TEOAE) at two sessions approximately 6-8 weeks apart; workers were characterized in groups by low, medium and high exposures to styrene concentrations. Although no significant dose-response relationship was found, a significantly elevated odds ratio for hearing loss was observed in the group who had chronic exposures to the highest levels for a duration of approximately 15 years or longer (Triebig, Bruckner, & Seeber, 2009). NIOSH conducted a re-evaluation of styrene and noise exposures in the fiberglass-reinforced plastic boat manufacturing industry. The report states that “health effects of low-level styrene exposure include ototoxicity in workers and experimental animals” (Hammond, 2007). Further, the report notes that “styrene has been shown to be a potent ototoxin by itself and can have a synergistic effect when presented together with noise or ethanol” (Hammond, 2007).

Jet Fuel

Jet fuel, or aviation kerosene, is a mixture of aromatics and additives with various components of different concentrations depending on the fuel type and purpose. Some of the compound mixture components may be unknown, particularly with military fuels. Jet fuel does not have a specific exposure limit in OSHA standards; however, common ingredients benzene, xylene, and toluene do have individual limits (OSHA). A literature review completed between 1993 and 2014 at University of Queensland evaluated electrophysiologic and/or behavioral assessments of central auditory dysfunction with exposures to jet fuel (aromatic solvent components, solely or in combination) and noise. Six studies met the final inclusion criteria of the literature review. Results suggested an
association between exposure to aromatic solvents, including jet fuel, and noise, and central auditory dysfunction and/or hearing loss. (Warner, Fuente, & Hickson, 2015).

Other Solvent Mixtures

Many industrial processes involve more than one organic solvent, exposing workers to various types and concentrations of ototoxic compounds. Gopal presented case studies from seven subjects exposed to toluene and/or xylene for at least three years or more, and completed a battery of peripheral and central auditory function tests. All subjects demonstrated central auditory pathway and/or retrocochlear abnormalities on one or more tests (2008).

Carbon Disulfide

Carbon disulfide (CS₂) is a flammable, colorless liquid that evaporates in the air; the absorption pathway in humans is inhalation. It is used in a variety of industries to make rayon, cellophane, and carbon tetrachloride. It is also used to dissolve rubber and serves as raw material for some pesticides (ATSDR, 1996). Male workers from a manufacturing plant exposed to CS₂ were placed into three subject groups: CS₂ and hazardous noise exposure, hazardous noise-only exposure, and a low-noise (less than or equal to 85 dBA) exposure group. Hearing thresholds were gathered from each group in addition to a demographic and lifestyle questionnaire. The authors note an increased adjusted odds ratio of hearing loss with increasing CS₂ dose; additionally, the results suggest a synergistic effect with more hearing loss than is predicted with noise alone (Chang et al., 2003).

Solvent Mixtures and Interactions with Noise

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Many manufacturing facilities use more than one organic solvent in industrial processes, which may include several ototoxic substances in different concentrations. Additionally, concomitant exposure to noise, even at levels below OELs, can act synergistically with ototoxic chemicals to increase the effects on the auditory system. Much of the human research in solvent ototoxicity has been completed on workers exposed to both solvent mixtures and noise at various OELs.

Furniture manufacturing workers exposed to a solvent mixture containing xylene, n-hexane and toluene all below the permissible exposure level in Chile and measured average noise exposures < 85 dBA were compared to a medical faculty control group. The authors noted statistically significant differences on several behavioral measurements of central auditory system function and no statistically significant differences between pure tone thresholds for the two groups (Fuente, McPherson, Munoz, & Espina, 2006). Employees in a paint-and-lacquer factory exposed to a solvent mixture which included xylene and toluene below the occupational exposure limit in Poland and mean noise exposure <82 dBA were more likely to have a hearing impairment than the non-solvent exposed group.

Factory workers exposed to various solvent mixtures, largely toluene and methyl ethyl ketone, in the manufacturing of reinforced fabrics participated in a study that categorized subjects in three groups: minimal exposure, moderate and maximal exposure. Minimally exposed subjects included mostly administrative staff while the maximally exposed subjects included mostly factory floor staff. Noise levels measured in the factory
ranged from 74 to 84 dBA. Audiological evaluation included a medical risk factors and self-reported solvent and noise exposure questionnaire, pure-tone thresholds (including extended high frequency audiometry), and Dichotic Digits (DD). Performance on the DD test for the maximally exposed group was significantly lower than in the other two groups, although differences in threshold results across the groups were inconclusive (Fuente et al, 2009).

Paint factory workers exposed to low levels of organic solvents and noise (all sampled exposures were below the OSHA PEL) were compared to non-exposed workers by pure-tone thresholds through 16,000 Hz and by ABR. Hearing thresholds were increased (worse) and there were greater absolute and interpeak latencies on the ABR for the exposed subjects (Juarez-Perez, Torres-Valenzuela, Haro-Garcia, Borja-Aburto, & Aguilar-Madrid, 2014).

Although evidence of vestibular effects from solvent mixtures is limited in humans, balance testing (electronystagmography and posturography) noted abnormalities in the solvent-exposed group affecting the central vestibular system as well as postural control and coordination (Zamyslowska-Szmytke, et al., 2011).

Metals

Ototoxicity caused by environmental exposures is not limited to solvents. The literature describes human and animal studies correlating auditory damage with metal exposure, primarily lead. Some metals, such as lead and mercury, have not only been
found to cause auditory damage but also cognitive deficits by crossing the blood-brain barrier and fetal development issues by traveling through the placenta. Initial pathways to the human body include ingestion, inhalation, and dermal exposure (ATSDR, 2012a; Hoshino et al., 2015; Roth & Salvi, 2016).

**Lead**

Arguably, lead is the most researched metal with regards to adverse health effects primarily due to lead-based paints produced through the 1970s. Currently, lead exposure occurs occupationally from the manufacture and reclamation of lead-acid batteries, mining operations, ammunition, and industrial paints. Exposure to lead can also be from recreational activities such as pistol shooting and remodeling in older homes. Children are particularly susceptible to lead from contaminated soil, paint chips, or from water in old homes with lead solder (ATSDR, 2007a). Lead has been found to induce hearing damage in humans and animals. Elevated pure-tone thresholds have been linked to blood-lead levels (BLLs) in children (Schwartz & Otto, 1987), and in adults, BLLs have been significantly associated with high-frequency hearing loss (Ghiasvand et al., 2016). With lead-based paints and other occupational uses banned in 1978, remaining sources of lead exposure today include structures built prior to that point, but also firing ranges where lead bullets pose an exposure risk through both combustion materials and the projectile itself. The National Academies of Science released a study of Department of Defense (DoD) firing ranges in 2012 which showed personnel working in firing range environments with high potential for inhalation of air-borne lead particles had the highest BLLs,
predominantly in shoot houses as well as maintenance and cleaning activities (National Research Council, 2012).

**Arsenic**

Arsenic occurs naturally in Earth’s soil, and exists in both organic and inorganic forms. Exposure to arsenic most commonly occurs via contaminated water and seafood (organic), but can also be found in mining and ore-smelting operations (inorganic) (ATSDR, 2007b). Although currently restricted, arsenic has been used in pesticides and wood preservatives (CDC, 2013). There are human and animal studies which have documented auditory damage due to arsenic exposure. Specifically, a study examining hearing thresholds among 10-year old children exposed to inorganic arsenic fumes from a neighboring power plant discovered statistically significant hearing loss compared to a control group of age-matched peers (Bencko et al., 1977). The degree of hearing loss varied, and was most prominent at 125, 250, and 8000 Hz. In China, inhabitants of a village with inorganic arsenic-contaminated drinking water were found to have statistically significant hearing loss, taste loss, blurred vision, peripheral neuropathy, and hypertension compared to a village without chronic arsenic toxicity (Guo et al., 2007). Animal studies have demonstrated damage to anatomical structures within the cochlea, including degeneration of Reissner’s membrane, mitochondria and cytoplasm cell injury, microvilli loss, and epithelial cell depression in the stria vascularis after acute atoxyl (organic arsenic compound) intoxication (Anniko, 1976a; Anniko, 1976b).
**Barium**

The amount of barium found naturally in the environment is generally insignificant; however, contaminated water and soil can lead to high amounts of barium in drinking water, Brazil nuts, seaweed, and fish. Environmental contamination can occur near industrial sites using barium compounds, and population exposure through inhalation and/or ingestion by workers and any people living near the worksite (ATSDR, 2007c).

Few studies have investigated the effects of barium on the auditory system. Ohgami et al (2016) examined the association between barium levels and pure-tone thresholds (at frequencies 1000, 4000, 8000, 12000 Hz) in humans. They found statistically significant associations between barium levels and pure-tone thresholds, with the strongest association identified at 8000 Hz and 12000 Hz where the subjects’ thresholds were in the mild to moderate hearing-loss ranges.

**Cobalt**

Cobalt is a naturally occurring element that exists in small amounts in water, soil, rocks, plants, and animals. Cobalt metal is often combined with other metals to create alloys. Cobalt can be used in the manufacturing of aircraft engines, magnets, grinding and cutting tools, as well as artificial hips and knee joints. Cobalt compounds are utilized in glass colorants, ceramics, paints, and paint driers (ATSDR, 2004). Evidence of auditory damage due to cobalt toxicity is scarce and is limited to human case reports and one study performed on rabbits. Human case reports of hearing loss due to extreme cobalt exposure occupationally, and from prosthetic hip replacements, have described blindness and
peripheral neuropathy (Oldenburg et al, 2009; Steens et al, 2006; Rizzetti et al, 2009; Paustenbach et al, 2013; Bradberry et al, 2014). Interestingly, an animal study conducted with rabbits (Apostoli et al., 2013) also noted clinical deafness, as well as blindness and peripheral neuropathy. Histopathological examination of these rabbits revealed both inner and outer hair cell loss in the cochlea, with more severe depletion of the outer hair cells than the inner hair cells.

Mercury

Mercury is naturally present in low levels in air, water, and food. Exposure to hazardous levels of mercury can occur via contaminated food and water supplies, as well as by means of inhalation of mercury vapors. Mercury compounds and vapors may pose a risk to workers in the following settings: chemical processing plants, mercury mines, thermometer manufacturing, electrical switch manufacturing, fluorescent light bulb manufacturing, fossil fuel power plants, cement manufacturing, battery manufacturing, and dental professionals (Johnson & Morata, 2010; EU-OSHA, 2009; ATSDR, 1999b).

Mercury accumulates in fish, some more than others, in the form of methylmercury. Fish living in mercury-contaminated waters can harbor high levels of mercury. Due to the ability of methylmercury to pass through the bloodstream from pregnant women to developing fetuses, and through the breast milk of nursing mothers to infants, recommendations are given to pregnant and nursing women to avoid fish containing high levels of mercury. Examples of fish known for high mercury levels can include (but not
limited to) shark, swordfish and any fish taken from bodies of water that have high levels of mercury.

Mercury poisoning was associated with hearing loss in individuals in Minimata, Japan through fish consumption (Harada, 1995). Abnormal ABRs were observed in humans exposed to mercury in numerous studies (Moshe et al., 2002; Counter et al., 1998; Discalzi et al., 1993). Counter et al. (1998) also found mildly abnormal hearing thresholds in children and mild-to-severely abnormal hearing thresholds in adults who consumed mercury-contaminated food, within the same study population who exhibited the abnormal ABRs. This particular study group had a mean mercury level over five-times that of the unexposed control group.

Tin, Organic Compounds

Three main applications for organic compounds of tin (commonly referred to as organotin) are heat stabilizers, catalysts, and biocides (Ross, 1965). These compounds are utilized in PVC and plastic manufacturing, the glass industry, industrial manufacturing of tin cans and containers, agricultural fungicides for wood treatment, antifouling paints, and pesticides for fruits, vines, hops, cotton, vegetables, cotton, and ornamentals (ATSDR, 2005; NPI, 2014). Other than animal studies linking trimethyltin and triethyltin to auditory damage (Fetcher & Carlisle, 1990; Young & Fetcher, 1986), only one human report was found, in which six industrial workers exposed to trimethyltin suffered acute limbic-cerebellar syndrome, including symptoms of hearing loss and disorientation (Besser et al., 1987).
Cadmium

Occupationally, cadmium compounds are incorporated in the manufacturing of electroplates, pigments, alkaline batteries, glass, silver-zinc storage batteries, heat stabilizers for plastics and alloys, and cement. Cadmium is also released in mining, smelting, and metal-ore refining operations (Huff et al., 2007). Non-occupationally, the primary source of cadmium exposure to humans is by ingestion of certain foods such as leafy vegetables, potatoes, grains, peanuts, soybeans, and sunflower seeds. High levels of cadmium can be found in tobacco leaves. Smoking almost doubles the amount of cadmium intake in humans (ATSDR, 2012a). In humans, high blood cadmium levels have been associated with significantly higher pure-tone threshold averages, as well as significantly higher age-adjusted geometric mean blood levels in participants with hearing loss compared to those without hearing loss (Choi et al., 2012). Another study revealed significantly higher odds of low-frequency hearing loss in individuals with high urinary cadmium levels compared to those with low urinary cadmium levels (Shargorodsky et al., 2011).

Manganese

Manganese is present in rocks and soil, and as such, it is found naturally in many foods. Manganese is necessary for human health and is often included in vitamin supplements. Like many elements, too much manganese can be hazardous. High-level exposures can occur in welding shops, steel factories, mining operations, and automobile maintenance shops (ATSDR, 2012b). Additionally, manganese exposure can occur in the
manufacturing of dry-cell batteries, electrical coils, ceramics, matches, glass, fertilizers, and animal food additives (EU-OSHA, 2009). A review of animal studies, human case reports, and human studies suggests ototoxic effects from manganese exposure; however, the studies offered weak evidence. For example, hearing loss has been found among some workers occupationally exposed to strong concentrations of manganese and noise; however, due to study limitations (noise exposure, age, and smoking confounders) it is unclear whether the manganese exposure actually contributed to the hearing loss (Nikolov, 1974; Bouchard, 2008).

**Asphyxiants**

Unlike the chemicals discussed above, vapors or gases known as asphyxiants have not demonstrated permanent hearing loss alone, but rather have only been shown to potentiate the effects of noise. Moreover, they are the most common occupational ototoxic chemicals, yet are also just as likely to be found in non-occupational settings (Johnson & Morata, 2010; Fechter, et al., 2002), making asphyxiants particularly high-risk chemicals when found in combination with noisy environments. It is important to note that, like potentially ototoxic metals, asphyxiants are under-represented in the literature for ototoxic effects in general and offer no human studies to date. Studies in animals have noted the following substances as potentially ototoxic in the presence of noise: carbon monoxide (CO) (Lund & Krsitiansen, 2004; Rao & Fechter, 2000; Chen & Fechter, 1999; Chen, et al., 1999; Fechter, Young & Carlisle, 1988; Young et al., 1987; Fechter, et al., 1987), hydrogen cyanide, (Fechter, et al., 2002; Fetcher, et al., 2002), and nitriles (Fechter, et al., 1987).
2004; Fechter et al, 2003; Pouyatos et al., 2005; Pouyatos et al, 2007, Johnson & Morata, 2010), the latter most commonly found in man-made industrial chemicals.

The most common asphyxiant exposure is likely carbon monoxide (CO). CO is a globally pervasive air pollutant created as a by-product of combustion. Occupational as well as recreational/lifestyle exposures are common: for example, people can be exposed to CO during a day on the job in a factory with an internal combustion engine-powered machine or a bike ride along the highway to and from that job. Additionally, CO is one of the noxious elements found in tobacco smoke. Engine exhaust, cigarette smoke and other CO sources like metallurgy and wood fires makes it the most prevalent ototoxic chemical exposure (NIOSH, 1972; Hosey, 1970). The research showing hearing loss effects as a result of exposure to this ubiquitous chemical, however, is limited to rodent models where results clearly show no effect when exposed to chronic CO alone but a strong potentiation effect on noise-induced hearing loss (Lund & Krsitiansen, 2004; Rao & Fechter, 2000; Chen & Fechter, 1999; Chen et al., 1999; Fechter et al., 1988; Young et al., 1987). Only with acute, high dose injections of CO were effects of temporary hearing loss demonstrated (Fechter, Thorne & Nuttall, 1987).

More information related to human exposure is needed, yet is difficult to obtain as intentional exposure to asphyxiants would be highly unethical due to their many other adverse health effects. Based on animal data, it is worth noting that acceptable levels (based on international OELs are well below those shown to cause an auditory injury alone or in combination with noise with any of these agents in the animal models studied (Johnson &
Morata, 2010; Fechter et al., 2002). However, exposures are still common – e.g., hydrogen cyanide is found in steel, electroplating, mining, chemical industries, metal leaching operations, metal cleaning, and analytical chemistry occupations and it is used in the manufacture of synthetic fibers, plastics, dyes, pigments, and nylon (Fetcher, Chen, & Rao, 2002), thus warranting consideration of additional education, monitoring, and protection for populations exposed with noise.

Discussion

Summary

Table 16 summarizes key information for clinical diagnosis, including the exposure pathway, typical sources or products, current exposure limits, and the ototoxic effects demonstrated in human studies literature of non-pharmaceutical agents. For full reviews of chemicals without human evidence, see Johnson & Morata (2010) or Vyskocil et al. (2012). Note that none of the exposure limits listed are based upon ototoxic effects, but rather other effects such as neurotoxicity. When looking to reduce the number of significant threshold shifts in employees, exposure to ototoxins may need to be controlled well below the permissible levels.
Table 16. Summary of Ototoxins and Their Exposure Limits

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Exposure Pathway</th>
<th>Recognized as Ototoxic by Agencies</th>
<th>Exposure Limits</th>
<th>Ototoxic Effect</th>
<th>Typical uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>Inhalation</td>
<td>OSHA, The Noise Manual ATSDR European Agency for Safety and Health at Work, The Nordic Expert Group, Category 1*</td>
<td>General Industry: 200 ppm TWA, 300 ppm C; exception: exposure may exceed 300 ppm, but not more than 500 ppm (Peak) for a single time period up to 10 minutes for any 8-hour shift Construction Industry: 200 ppm, 750 mg/m³ TWA Maritime: 200 ppm, 750 mg/m³, 100 Skin CAL OSHA PEL: TWA 10 ppm, 37 mg/m³, ceiling 500 ppm, ST 150 ppm, 560 mg/m³, Skin NIOSH REL: 100 ppm, 375 mg/m³ 10-hour TWA; 150 ppm, 560 mg/m³ ST NIOSH IDLH: 500 ppm (OSHAe)</td>
<td>Chronic exposure to average concentrations as low as 50-130 ppm damages hearing and color vision. Neurological component and potential damage to cochlear hair cells (ATSDR, 2005)</td>
<td>Paints, paint thinners, fingernail polish, lacquers, adhesives, rubber, gasoline, printing, leather tanning (OSHAe)</td>
</tr>
<tr>
<td>Substance</td>
<td>Route</td>
<td>OSHA, The Noise Manual ATSDR</td>
<td>European Agency for Safety and Health at Work, The Nordic Expert Group, Category 2*</td>
<td>OSHA PEL: 100 ppm TWA CAL OSHA PEL: 5 ppm; 30 ppm (ST) NIOSH REL: 100 ppm, 125 ppm (ST) (OSHAc)</td>
<td>Low concentrations for several days to weeks resulted in irreversible damage to inner ear and hearing of animals (ATSDR, 2010a)</td>
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<tr>
<td>Ethylbenzene</td>
<td>Inhalation</td>
<td></td>
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</tr>
<tr>
<td>n-propylbenzene</td>
<td>Inhalation, skin</td>
<td>OSHA, The Noise Manual European Agency for Safety and Health at Work</td>
<td>None specified</td>
<td></td>
<td>Fuel and fuels additive, solvent manufacture (NCBi)</td>
</tr>
<tr>
<td>Styrene</td>
<td>Inhalation</td>
<td>OSHA, The Noise Manual ATSDR</td>
<td>European Agency for Safety and Health at Work, The Nordic Expert Group, Category 1*</td>
<td>OSHA PEL: 100 ppm; 200 ppm © OSHA Max Level in 8 hour period: 600 ppm, 5 min in any 3 hour period OSHA Construction: (C) 100 ppm; (C) 420 mg/m3 CAL OSHA PEL: 50 ppm; 100 ppm (ST); 500 ppm © NIOSH REL: 50 ppm; 100 ppm (ST) (OSHAb: OSHAd)</td>
<td>Human and animal studies Cochlear damage, neurotoxicity (ATSDR, 2010b)</td>
</tr>
<tr>
<td>Substance</td>
<td>Route of Exposure</td>
<td>OSHA, The Noise Manual</td>
<td>European Agency for Safety and Health at Work</td>
<td>OSHA: 100 ppm (C); 480 mg/m³ ©</td>
<td>OSHA Construction: 100 ppm (C); 480 mg/m³ ©</td>
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</tr>
<tr>
<td>alpha-Methyl styrene</td>
<td>Inhalation</td>
<td>OSHA, The Noise Manual</td>
<td>European Agency for Safety and Health at Work</td>
<td>OSHA PEL: 100 ppm; 200 ppm (C)</td>
<td>OSHA Max Level in 8 hour period: 300 ppm, 5 min in any 2 hour</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>Inhalation, Skin</td>
<td>OSHA, The Noise Manual</td>
<td>European Agency for Safety and Health at Work, The Nordic Expert Group, Category 2*</td>
<td>OSHA PEL: 100 ppm; 435 mg/m³</td>
<td>CAL OSHA: 100 ppm; 150 ppm (ST); 300 ppm (C)</td>
</tr>
<tr>
<td>p-Xylene</td>
<td>Inhalation</td>
<td>OSHA, The Noise Manual</td>
<td>European Agency for Safety and Health at Work, The Nordic Expert Group, Category 2*</td>
<td>OSHA PEL: 100 ppm; 435 mg/m³</td>
<td>CAL OSHA: 100 ppm; 150 ppm (ST); 300 ppm (C)</td>
</tr>
</tbody>
</table>

Table 16 (continued)
Table 16 (continued)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Route of Exposure</th>
<th>Source</th>
<th>OSHA PEL</th>
<th>OSHA Construction</th>
<th>CAL OSHA</th>
<th>NIOSH</th>
<th>Hearing Loss</th>
<th>Solvent Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Hexane</td>
<td>Inhalation</td>
<td>OSHA, The Noise Manual ATSDR European Agency for Safety and Health at Work, The Nordic Expert Group, Category 3*</td>
<td><strong>OSHA PEL:</strong> 500 ppm; 1800 mg/m³ <strong>OSHA Construction:</strong> 500 ppm; 1800 mg/m³ <strong>CAL OSHA:</strong> 50 ppm <strong>NIOSH:</strong> 50 ppm <em>(OSHa; OSHAc)</em></td>
<td>Hearing loss in animal studies; reported with human studies <em>(ATSDR, 1999a)</em></td>
<td>Solvent used in laboratories, used to extract vegetable oils from crops, found in cleaning agents for printing, textile, furniture and shoemaking industries, also in adhesives <em>(ATSDR, 1999a)</em></td>
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<tr>
<td>Carbon disulfide</td>
<td>Inhalation, Skin</td>
<td>OSHA, The Noise Manual ATSDR European Agency for Safety and Health at Work, The Nordic Expert Group, Category 1*</td>
<td><strong>OSHA PEL:</strong> 20 ppm; 30 ppm <em>(C)</em> <strong>OSHA Max Level in 8 hour period:</strong> 100 ppm for 30 min <strong>OSHA Construction:</strong> 20 ppm 60 mg/m³ <strong>CAL OSHA:</strong> 1 ppm; 12 ppm <em>(ST)</em>; 30 ppm <em>(C)</em> <strong>NIOSH REL:</strong> 1 ppm; 10 ppm <em>(ST)</em> <em>(OSHAa)</em></td>
<td></td>
<td>Used in manufacture of rayon, cellophane, and carbon tetrachloride; used to dissolve rubber to produce tires and is in some pesticides <em>(ATSDR, 1996)</em></td>
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<tr>
<td>Lead inorganic</td>
<td>Environmental exposure is both oral and inhalation, particularly children</td>
<td>OSHA, The Noise Manual ATSDR, The Nordic Expert Group, Category 1*</td>
<td><strong>OSHA PEL:</strong> 0.05 mg/m³; reduced exposure limit for work days beyond 8 hours <strong>CAL OSHA:</strong> 0.05 mg/m³ <strong>NIOSH REL:</strong> 0.05 mg/m³ <em>(OSHAf; OSHAo)</em></td>
<td>Epidemiological studies have found SNHL with chronic exposure to lead. Children have been found to have decreased hearing with blood lead levels. Linear relationship between blood lead levels and decreased hearing. <em>(ATSDR, 2007b)</em></td>
<td>Manufacture of batteries, non-drinking water plumbing, paints, dyes, ceramic glazes, ammunition; Mining industry; Used in sheets to protect from radiation; May be found in some gasoline; Children can ingest contaminated soil, paint chips or from water in old homes. <em>(ATSDR, 2007b)</em></td>
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### Table 16 (continued)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Inhalation</th>
<th>Standard</th>
<th>Regulatory</th>
<th>Health Effects</th>
<th>Exposure Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mercury</strong></td>
<td>ATSDR, The Nordic Expert Group, Category 1*</td>
<td>OSHA: 0.1 mg/m³ (C) &lt;br&gt; CAL OSHA: 0.025 mg/m³ (for metallic and inorganic) &lt;br&gt; NIOSH REL: 0.05 mg/m³ (OSHAc)</td>
<td>Mild to moderately-severe hearing loss in humans (Counter et al., 1998) &lt;br&gt; Abnormal ABRs in humans (Moshe et al., 2002; Counter et al., 1998; Discalzi et al., 1993)</td>
<td>Neurotoxin caused reports of hearing loss, balance issues with humans. (ATSDR, 1999b)</td>
<td>Occupational exposure to mercury include manufacture of electrical equipment, automotive parts, chemical processing, construction, medical professions. Environmental exposures due to common products like thermometers, and electrical switches. Diets high in fish due to methyl mercury in fresh and saltwater. (ATSDR, 1999b)</td>
</tr>
<tr>
<td><strong>Cobalt</strong></td>
<td>Inhalation</td>
<td>OSHA PEL: 0.1 mg/m³ &lt;br&gt; CAL OSHA: 0.02 mg/m³ &lt;br&gt; NIOSH REL: 0.05 mg/m³ (OSHAc)</td>
<td>Varying degrees of hearing loss noted in human case reports of extreme cobalt toxicity occupationally and from prosthetic hip replacements (Oldenburg et al., 2009; Steens et al., 2006; Rizzetti et al., 2009; Paustenbach et al., 2013; Bradberry et al., 2014)</td>
<td>Clinical deafness in animal study, with histopathological exam revealing both inner and outer hair cell depletion (Apostoli et al., 2012)</td>
<td>Hard metal industry, coal mining, metal mining, smelting and refining. Cobalt dye painters and cobalt chemical production (ATSDR, 2004)</td>
</tr>
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Table 16 (continued)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Route of Exposure</th>
<th>Agency</th>
<th>OSHA PEL</th>
<th>CAL OSHA</th>
<th>NIOSH REL</th>
<th>Description</th>
<th>Exposure Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barium, soluble compounds</td>
<td>Inhalation</td>
<td>ATSDR</td>
<td>OSHA PEL: 0.5 mg/m³</td>
<td>CAL OSHA: 0.5 mg/m³</td>
<td>NIOSH REL: 0.5 mg/m³</td>
<td>In a human study, statistically significant associations between barium levels and pure-tone thresholds at frequencies 1000Hz, 4000Hz, 8000Hz, and 12000Hz, with the strongest associations at 8000Hz and 12000Hz (Ohgami et al., 2016)</td>
<td>Oil and gas drilling, used in paint, bricks, ceramics, glass and rubber (ATSDR, 2007a)</td>
</tr>
<tr>
<td>Arsenic, Inorganic compounds</td>
<td>Inhalation</td>
<td>ATSDR</td>
<td>OSHA PEL: 0.5 mg/m³</td>
<td>CAL OSHA: 0.5 mg/m³</td>
<td>NIOSH REL: Ca 0.002 mg/m³ (C) [15 min]</td>
<td>Low-frequency hearing loss in children (ATSDR, 2007b)</td>
<td>By-product of smelting copper, lead, cobalt, and gold ore. Wood preservation, lead-acid batteries, semi-conductors and light emitting diodes (ATSDR, 2007b)</td>
</tr>
<tr>
<td>Arsenic, Organic compounds</td>
<td>Inhalation</td>
<td>ATSDR</td>
<td>OSHA PEL: 0.5 mg/m³</td>
<td>CAL OSHA: 0.2 mg/m³</td>
<td>NIOSH REL: 0.1 mg/m³ except cyhexatin</td>
<td>Human case report of 6 industrial workers who experienced hearing loss and disorientation (Besser et al., 1987)</td>
<td>Pesticides (usually for cotton) (ATSDR, 2007b)</td>
</tr>
<tr>
<td>Tin, Organic compounds</td>
<td>Inhalation</td>
<td>ATSDR</td>
<td>OSHA PEL: 0.1 mg/m³</td>
<td>CAL OSHA: 0.1 mg/m³</td>
<td>NIOSH: 0.1 mg/m³ except cyhexatin</td>
<td>High frequency hearing loss in rats, guinea pigs with trimethyltin. Disrupts function at synapse between inner hair cell and type I spiral ganglion</td>
<td>Manufacture of plastics, food packages, plastic pipes, pesticides, paints, and pest repellents (ATSDR, 2005)</td>
</tr>
<tr>
<td>Substance</td>
<td>Route of Exposure</td>
<td>Source</td>
<td>OSHA PEL:</td>
<td>Other Regulations</td>
<td>Toxicological Effects</td>
<td></td>
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<tr>
<td>Carbon Monoxide</td>
<td>Inhalation</td>
<td>OSHA, The Noise Manual</td>
<td>50 ppm; 55</td>
<td>CAL OSHA: 25 ppm;</td>
<td>Potentiates noise-induced hearing loss in rats and rabbits; Does not cause by chemical</td>
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<td></td>
<td></td>
<td>ATSDR</td>
<td>mg/m³</td>
<td>250 ppm (C)</td>
<td>exposure alone. (ATSDR, 2012c)</td>
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<td>NIOSH REL: 35 ppm; 200</td>
<td></td>
<td>(C) OSHA: 0.025 mg/m³ (AL) CAL OSHA: 0.005 mg/m³ NIOSH: Ca (See Appendix A) (OSHAc)</td>
<td>Exposure to incomplete combustion particularly in enclosed or poorly ventilated spaces. Used in industry to synthesize compounds (ATSDR, 2012c)</td>
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<td>NIOSH REL:</td>
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<td></td>
<td>1 mg/m³, 3 mg/m³ (ST) OSHA: 5 mg/m³ (C) CAL OSHA: 0.2 mg/m³ NIOSH REL: 1 mg/m³, 3 mg/m³ (ST) (OSHAc)</td>
<td>Byproduct of production of other metals such as zinc, lead, or copper. Battery recovery. (ATSDR, 2012a)</td>
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<tr>
<td>Cadmium</td>
<td>Inhalation</td>
<td></td>
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<td>Positive association between higher (poorer) pure-tone threshold averages in humans with high blood cadmium levels (Choi et al., 2012). Higher odds of low-frequency hearing loss in humans with high urinary cadmium levels (Shargorodsky et al., 2011).</td>
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<td>Limited case studies suggest hearing loss in humans (Nikolov, 1974; Bouchard, 2008) Animal studies revealed significant damage to inner and outer hair cells, peripheral auditory nerve fibers and spiral ganglion neurons (Ma et al., 2008; Ding et al., 2011).</td>
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<td>Steel production; may be found in brazing rods in addition to stainless steel, high-temperature steel, tool steel, cast iron, and super alloys (ATSDR, 2012b)</td>
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<tr>
<td>Manganese compounds</td>
<td>Inhalation</td>
<td>The Nordic Expert Group,</td>
<td>75 ppm, 350</td>
<td>OSHA: 75 ppm, 350</td>
<td>Affects central nervous system. (ATSDR, 1990)</td>
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<td></td>
<td></td>
<td>Category 3*</td>
<td>mg/m³</td>
<td>mg/m³</td>
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<td>CAL OSHA: 10 ppm</td>
<td>Manufactured for use as a solvent and is used in the production of other chemicals (ATSDR, 1990)</td>
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<tr>
<td></td>
<td></td>
<td>NIOSH REL: none, but</td>
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<td>NIOSH TWA is adequate</td>
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<tr>
<td></td>
<td></td>
<td>question if OSHA TWA is adequate (OSHAc; NIOSH, 2016)</td>
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**Table 16 (continued)**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Routes of Exposure</th>
<th>Expert Group</th>
<th>OSHA PEL</th>
<th>CAL OSHA</th>
<th>NIOSH REL</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Heptane</td>
<td>Inhalation</td>
<td>The Nordic Expert Group, Category 3*</td>
<td>OSHA PEL: 500 ppm, 2000 mg/m³</td>
<td>CAL OSHA: 400 ppm, 500 ppm (ST)</td>
<td>NIOSH REL: 85 ppm, 440 ppm (ST) (15-min)</td>
<td>Component of JP-8 (Jet fuel); paint additive and coating additive, solvent; found in adhesives, sealants, ink, toner colorant products, automotive care products (NCBIc)</td>
</tr>
<tr>
<td>Polychlorinated Biphenyls (PCBs) as Chlorodiphenyl (42% and 54% chlorine)</td>
<td>Inhalation, Skin, Ingesting PCB-contaminated food (sportfish, wildlife) (ATSDR, 2000)</td>
<td>The Nordic Expert Group, Category 3*</td>
<td>42% Chlorine OSHA PEL: 1 mg/m³ CAL OSHA: 1 mg/m³ NIOSH REL: Ca 0.001 mg/m³</td>
<td>54% Chlorine OSHA PEL: 0.5 mg/m³ CAL OSHA: 0.5 mg/m³ NIOSH REL: Ca 0.001 mg/m³ (OSHAc)</td>
<td>Rats - Low frequency hearing loss from perinatal exposure (ATSDR, 2000)</td>
<td>Manufacture of PCBs stopped in U.S. in August 1977. Used as coolants and lubricants in transformers, capacitors, and other electrical equipment. (ATSDR, 2000)</td>
</tr>
</tbody>
</table>
Table 16 (continued)

<table>
<thead>
<tr>
<th>Cyanides (as CN)</th>
<th>Inhalation</th>
<th>Occupational: Inhalation; unlikely in the U.S. (ATSDR, 2014b)</th>
<th>The Nordic Expert Group, Category 2*</th>
<th>OSHA PEL: 5 mg/m³ CAL OSHA: 5 mg/m³ NIOSH REL: 5 mg/m³ (C), (10-min) (OSHAc)</th>
<th>Cyanogen glycosides has neurological effects and show hearing difficulties but may be due to other components in diet. Exposure to cyanide with noise cause a hydrogen cyanide-dose-related increase in auditory compound action potential thresholds in rats (ATSDR, 2006)</th>
<th>Cyanide salts and hydrogen cyanide are used in electroplating, metallurgy, organic chemical production, photographic developing, manufacture of plastics, fumigation of ships, and some mining processes (ATSDR, 2006)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhalation</strong> Dietary from cassava root and other fruits and vegetables (ATSDR, 2006)</td>
<td><strong>Occupational:</strong> Inhalation; unlikely in the U.S. (ATSDR, 2014b)</td>
<td>OSHA PEL: 0.1 mg/m³ CAL OSHA: 0.1 mg/m³ NIOSH REL: 0.05 mg/m³ (OSHAc)</td>
<td>Neurotoxin, long-term exposure of agricultural workers suggest low to moderate amounts of parathion may cause hearing loss (ATSDR, 2014b)</td>
<td>* The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (Johnson &amp; Morata, 2010). Authors outline three categories of evidence for ototoxic exposures: Category 1, human data indicate auditory effects under or near existing occupational exposure limit (OELs); there are also robust animal data supporting an effect on hearing from exposure; Category 2, human data are lacking whereas animal data indicate an auditory effect under or near existing OELs; Category 3, human data are poor or lacking; animal data indicate an auditory effect well above existing OELs.</td>
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</table>
Although no conclusive list of non-pharmaceutical ototoxic agents exists, audiometric monitoring program professionals (audiologists and physicians) should consider audiometric monitoring for workers exposed to known or suspected ototoxins in isolation and with concurrent noise exposure. Industrial hygienists and safety professionals should be highly cognizant of known and suspected ototoxins, worker’s measured exposures, as well as noise exposure levels, and ensure adherence to environmental and administrative controls. Workers exposed to noise and ototoxins below the OELs may also be at-risk for auditory damage, and this should be considered when developing monitoring criteria. OSHA, the American Conference of Governmental Industrial Hygienists (ACGIH), the United States (US) Army, and the US Air Force, among other federal and national agencies and organizations, have developed recommendations or information on ototoxicity which can be used as guidance (USAFSAM, 2016; Army, 2015; OSHAa; ACGIH, 2011).

Research Gaps

Solvents certainly make up the bulk of literature on non-pharmaceutical ototoxic agents. Unfortunately, dose-response relationships between occupational exposure levels and auditory pathway damage are still largely unknown. Perhaps even more germane, human studies are still needed to confirm the ototoxicity of many organic solvents, metals, and asphyxiants currently only supported by animal research. Due to the paucity of studies characterizing dose-response relationships, especially in human cohorts, the amount of
chemical exposure required to cause auditory dysfunction is not well known, nor is the severity of the auditory damage caused by the exposure. Without known dose-response characteristics of specific substances, it is difficult to hypothesize appropriate exposures with which to conduct animal experiments, and, even more challenging, to determine worksite exposure auditory hazards. This proves to be a challenging research caveat as some investigators acknowledge the exposure levels in their studies may be too low to elicit auditory damage. Similarly, given the mechanistic likelihood and sparse research showing an additive or synergistic effect of noise and ototoxic agents, further research is certainly warranted to understand the mechanisms and determine safe exposure levels for workers.

Hearing conservation programs monitor the peripheral auditory system through gold-standard pure-tone audiometric monitoring, although organic solvents, for example, often primarily affect the auditory nervous system. If future research demonstrates cochlear damage in humans to specific concentrations of ototoxins, consideration of other monitoring methods, such as OAE may be appropriate. Significant human and animal research is needed in the assessment of vestibular pathway involvement, both peripheral and central, to understand the effects of organic solvents on balance function. For hearing conservation programs, this presents a larger challenge of detection methods for screening of balance issues in occupational settings.

Other long-term research gaps include the advancement of biomarker detection for hearing loss or balance loss from solvent and/or noise exposure; as well as the relationship of hearing loss or balance loss and occupational exposure to solvents and/or noise to
genetic factors. Worker population studies will need to include a comprehensive audiological test battery potentially consisting of OAE testing, extended high-frequency audiometry, acoustic immittance testing, central auditory system testing, and/or balance/vestibular function testing. Retrospective statistical analysis of such clinical data, as well as the worksite exposure data, will be needed in future studies as well.

Recommendations for Occupational Ototoxic Exposures

Weighing the evidence available – albeit, imperfect and incomplete – improvements seem warranted in surveillance programs, medical record documentation, education and training, and tracking exposure (both ototoxic substance and noise). The inclusion of workers exposed to potentially ototoxic chemicals into existing hearing conservation programs, whether or not they are exposed to noise, may perhaps be the most impactful change for occupational safety and protection from ototoxins. In order to accomplish more targeted monitoring of at-risk workers, significant research on damage-risk criteria is necessary. Identifying personnel exposed to the hazards discussed herein will be dependent upon organizational definitions of early warnings, which may include, but is not limited to:

1) the American Speech-Language-Pathology Association (ASHA) clinical ototoxicity monitoring recommendation of 20 dB decrease at any one test frequency, 10 dB decrease at any two adjacent test frequencies, or loss of response at three consecutive test frequencies;
2) NIOSH suggests the use of a 15dB or more change from a baseline exam 500 to 6000 Hz, and confirmed on a 14 hour noise-free follow up test within 30 days, as a trigger to enact protective measures to prevent hearing loss; or

3) the DoD uses early warning changes (at least 15dB change at 1000, 2000, 3000 or 4000 Hz in either ear) in personnel exposed to hazardous noise and/or ototoxic chemicals) (ASHA, 1994; DOEHRS User Manual; Franks et al, 1996).

By any reasonable definition, personnel flagged should, at a minimum, receive additional education regarding the hazardous exposures and their hearing, as well as reinforced training, and inspection of their personal protective equipment (PPE). Providing information regarding potentiation of noise-induced hearing loss due to concomitant exposure to ototoxic agents could easily be included in the periodic education requirements for personnel enrolled in hearing conservation programs. Ensuring that all workers as well as occupational health professionals are educated on the risks posed by ototoxic substances will be an important step towards addressing and minimizing these risks.

Workplace hazard assessments need to identify both ototoxin and noise risks, and document their source(s), type of noise and chemicals, and the measured dose of noise and each chemical. Specific exposure durations (such as numbers of days, weeks, and months) and specific exposure levels for ototoxic substances, with and without concurrent noise exposure, needs to be added to record-keeping procedures. Following the hierarchy of methods for hazard controls, removal of the source of the hazardous exposures from the workplace is preferable. Other means of reducing noise levels, through engineering or
administrative controls, is also recommended. Substitution of ototoxins with less hazardous chemicals is also recommended when possible. When removal or reduction of the hazard is not possible or adequate, implementation of new technical measures to minimize potential exposures to ototoxins through inhalation, ingestion, and/or dermal absorption is required. This may include the assessment of ventilation systems and collection of air-quality samples, personal protective clothing and/or devices, food/water sources, and contamination inspections. Wearing hearing protection when exposed to noise and ototoxins, even when noise levels are below the regulated threshold, can prevent the combined effects of noise and solvent exposure, provided that proper hearing protection is available. Additional worker protection verification measures, such as hearing protection fit-testing, should be conducted and documented in the employee’s record.

Clinical Recommendations

Currently, ototoxic exposures beyond the clinical realm of medications are often overlooked during the diagnostic case history. Ensuring the patient’s medical record documents and contains details regarding their reported source(s) of both noise and potentially ototoxic chemicals exposures, such as type, measured concentration, and amount of exposure time to is recommended. Based on the evidence from human studies as detailed above, workers exposed to specific organic solvents may be at-risk for central auditory and/or vestibular dysfunction and this information should be considered by the clinician while implementing their monitoring program and/or clinical test battery.
Given the evolving state of research and growing evidence in this area, it would also be helpful to establish relationships with corresponding public health and industrial hygiene offices to assist in awareness of the issue at hand, as well as to help obtain information and/or data pertaining to the ototoxic exposures, PPE, and worker education and training recommendations.

Finally, consideration should be given to expanding the diagnostic evaluation of any patient with reported exposed to ototoxic or potentially ototoxic chemicals. Such expansions may include questionnaires regarding symptoms of imbalance, vertigo or dizziness, and consideration of recreational activities and exposures that may add to hazard cumulative dose. Expansion of monitoring may include, depending of specific site of lesion targeted by the hazard: namely, OAE testing and extended high-frequency audiometry, electrophysiology and/or central auditory processing evaluations. Clinicians are encouraged to perform electrophysiological and or CAP screening tests on individuals exposed to substances with demonstrated neurotoxic effects, especially if the individual reports speech understanding difficulties despite normal pure-tone and OAE results. The standardization of these comprehensive tests is certainly needed for non-pharmaceutical ototoxin-exposed populations and will improve the ability of future investigators to further assess and hone appropriate testing protocols and best practices through further research.

Conclusion
The literature reveals certain solvents, metals, asphyxiants, and other chemicals as ototoxic in humans, while others have only proven ototoxic in animal models to date. However, given that animal studies have demonstrated similar sites of lesion and similar mechanisms of ototoxicity as those identified in other human studies, it is biologically plausible that these under-researched agents could be ototoxic to humans. Nonetheless, it is imperative to note that human research is limited, and thus certain chemicals should not yet be interpreted as firmly ototoxic in humans; rather, such agents should be considered potentially ototoxic. Potentially ototoxic substances are worthy of improved surveillance and further research to understand their ototoxic mechanisms, effects, and possible mitigation strategies. In light of the available evidence, supervisors, medical professionals, workers themselves, as well as the public at large should exercise caution and preventative measures for potential ototoxic exposures.

A triad approach of monitoring, protecting, and educating is needed for effective prevention of hearing loss. The DoD Hearing Center of Excellence (HCE) has developed and is currently implementing such a triad approach in their Comprehensive Hearing Health Program (CHHP), initially focusing on noise-induced hearing loss but intended for application to all hearing loss prevention requirements (HCE, 2016). Surveillance provides the objective picture of hearing loss and exposures; education increases knowledge of noise, ototoxins, hearing and hearing loss; and protection ensures all are equipped and knowledgeable about how and when to use hearing protection strategies. If one component is ignored, the probability of success is likely reduced. A comprehensive approach is
required to effectively reduce hearing loss, particularly when insults to the auditory system can come from such a variety of sources in our daily lives.
5.4.2 Protection for medication-induced hearing loss: the state of the science

Hammill, Tanisha L.; Campbell, Kathleen M. Protection for medication-induced hearing loss: the state of the science. International Journal of Audiology, submitted 16 Mar 2017: In review (permissions from the publisher, Taylor & Francis Online, will be sought after accepted).

Abstract

Objective: This review will summarize information from the literature and ClinicalTrials.gov regarding the development of pharmaceutical interventions (preventative or treatment options) for medication-induced ototoxicity.

Design: Currently published literature was non-systematically reviewed using PubMed and ClinicalTrials.gov to summarize the current state of the science. Details on the stage of development in the market pipeline are provided, along with targeted mechanisms of action and evidence for clinical safety and efficacy reported. This review is limited to agents that have been in or are approaching clinical trials.

Results: Vitamins and antioxidants are the most common agents currently evaluated for drug-induced ototoxicity intervention by targeting the oxidative stress pathway that leads to cochlear cell death and hearing loss. However, other strategies, including steroid treatment and reduction of ototoxic properties of the primary drugs, are discussed.

Conclusions: Retention of hearing during and after a life threatening illness is a major quality-of-life issue for patients receiving ototoxic drugs and their families. The goal of
patient care is to extend life duration and to retain quality of life. Certainly hearing is a major factor in regards to quality-of-life, and the agents discussed herein, while not mature enough at this point, offer great promise toward that goal.

**Introduction**

The term “ototoxic” can be used to refer to any source of non-mechanical damage to the ear, including several medications, many solvents, some heavy metals, and possibly select asphyxiants (see Hammill et al, 2016, in this edition); yet ototoxicity is most often used in the context of clinical, medication-induced hearing loss or vestibular dysfunction. The field of pharmaceutical interventions for noise-induced hearing loss (NIHL), a condition which is also largely a result of toxic metabolic cochlear changes, is worthy of its own review. As such, and, coupled with the paucity of research into any treatment modalities for other ototoxic injuries, this review focuses on the current state of the science for preventing or treating ototoxicity as most often seen in the clinical setting – induced by medications.

The two most common types of ototoxic drugs are 1) cancer-fighting agents, namely platinum-based chemotherapy drugs such as cisplatin and carboplatin, and 2) intravenously administered antibiotics, including aminoglycosides and the glycopeptide vancomycin which has been reported to exacerbate aminoglycoside-induced ototoxicity. For detailed evidence of the ototoxic properties of these agents, see reviews by Watts (2017) found in this edition as well as Campbell et al (2003) and Campbell & Fox (2016).
A basic summary of the ototoxic mechanisms of action theorized to cause hearing impairments and vestibular dysfunction is provided below (also see reviews in Campbell 2007).

Apoptosis, or cell death, is an essential process for the health of all aerobic forms of life (beings with cell respiration reliant upon oxygen). It is the natural detoxification process to remove aged or damaged cells, often to clear the way for new development. In the human inner ear, the latter is unfortunately not the case, as mammals cannot regenerate cochlear tissue. At the inter-cellular level, mitochondria most often create, as a by-product of electron transfer, reactive oxygen species (ROS). However, various oxidative stressors can trigger the production of excessive ROS; and can produce a type of ROS called free radicals which have an unpaired electron. To return to homeostasis, the free radical will take an electron from surrounding molecules which, in excess, can damage vital cell membrane lipids and proteins by “stealing” their electron; thus triggering cell death through either the extrinsic death receptor pathway or the intrinsic mitochondrial pathway (for more detail, see Wang et al, 2008 or Jin & El-Deiry, 2005).

Intrinsic defenses exist against pathologic ROS over production, normally keeping the apoptotic process in balance. However, during excessive ROS production secondary to a toxic exposure, the intrinsic system can become overwhelmed. If ROS production exceeds inherent or supplemented antioxidant detoxification capabilities and triggers intra-cochlear cell death pathways, cell death can occur, reducing auditory and/or vestibular functionality. Given the hypothesis that most ototoxic agents initiate damaging oxidative
stress, approaches for the prevention of ototoxicity-induced auditory sensory loss include targets all along the cell death cascade. These targets can include prevention of ROS initiation; neutralizing the damage inflicted by ROS-created free radicals, most notably to the cell membrane lipids; or blocking the subsequent triggers of intrinsic or extrinsic apoptosis prior to cell death (Huang, et al, 2000).

Protective interventions for each ototoxin are considered with the unique mechanisms of ototoxic action of the drug in mind, taking care not to decrease the therapeutic efficacy of the drug for its intended, often life-saving, purpose. Interventions found to limit the ototoxin’s therapeutic efficacy or further potentiate ototoxic effects cannot be considered (Oishi et al, 2014).

**Common Ototoxic Medications**

Cisplatin is one of the most effective tools against many solid tumor cancer types. Unfortunately, like most chemotherapeutic agents, cisplatin has a high incidence of side effects, including ototoxicity that can be seen in nearly all patients treated with higher dose regimens (Rybak et al, 2007). The cochlea sustains damage to the outer and inner hair cells as well as supporting spiral ganglion and stria vascularis cells (Campbell & Fox, 2016). The primary mechanism of action in each of these areas is thought to be the production of inter-cellular ROS, which can trigger the metabolic apoptotic pathway (Rybak et al, 2007; Jamesdaniel et al, 2016). Therefore, antioxidant approaches have been widely attempted to prevent apoptosis at the formative stage of ROS development, thus preventing all
downstream processes in the cell death cascade, with the ultimate aim to prevent hearing loss.

Aminoglycosides (most commonly tobramycin, gentamicin, amikacin and kanamycin) are a class of antibiotics approved for treatment of potentially life-threatening infections, especially those caused by gram-negative bacteria, including bacterial endocarditis, peritonitis, and line sepsis (Gilbert, 2005). While nephrotoxic side effects are generally reversible, severe ototoxic damage most often is not, which can lead to permanent hearing loss, vestibular dysfunction, or both (Lerner et al, 1986).

Agents In or Approaching Clinical Investigations to Mitigate Medication-Induced Ototoxicity (see Table 17)

The table below provides information discovered as of the submission date of this article (Jan 2017), including other pertinent pre-clinical information, but excluding NIHL trials. Targets investigated in clinical trials are in bold font.

Table 17. Summary of agents investigated for prevention or treatment of medication-induced ototoxicity in clinical trials.

<table>
<thead>
<tr>
<th>Investigated agent</th>
<th>Ototoxicity Target(s) (preclinical and clinical)</th>
<th>ClinicalTrials.gov Identifier*</th>
<th>Evidence for Safety and Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-lipoic acid</td>
<td>- aminoglycoside-induced&lt;br&gt;- carboplatin-induced hearing loss&lt;br&gt;- cisplatin-induced</td>
<td>NCT00477607</td>
<td>Conlon et al, 1999; Rybak et al, 1999; Husain et al, 2005; Martin, 2014</td>
</tr>
<tr>
<td>Drug</td>
<td>Syndrome/Induction</td>
<td>Study ID</td>
<td>References</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------</td>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Amifostine</td>
<td>- cisplatin-induced</td>
<td>NCT00003269</td>
<td>Duval and Daniel, 2012; Hensley et al, 2009</td>
</tr>
<tr>
<td>Ginkgo Biloba</td>
<td>- aminoglycoside-induced - noise-induced</td>
<td>NCT01139281</td>
<td>Le Bars &amp; Kastelan, 2000; McKenna et al, 2001; Cakil et al, 2012; Dias et al, 2015; Dias, 2010; Huang et al, 2007; Finkler et al, 2012; Fukaya 1999; Ma et al, 2015</td>
</tr>
</tbody>
</table>
Antioxidants and Vitamins

**Vitamins with magnesium**

To date, animal work using vitamins A (specifically, beta carotene, the precursor to vitamin A), C, and E, combined with magnesium (ACE Mg) for otoprotection seems promising (Le Prell et al., 2007). Clinical trials have only occurred for noise-induced hearing loss but preclinical work suggests that this combination may also reduce aminoglycoside-induced ototoxicity (Le Prell et al., 2014). However, this combination cannot be safely used in smokers because beta carotene may increase the risk of lung cancer.
(Omenn, 1998 & 2007) and may be problematic in individuals with gastric disorders because of the Mg content. Thus, even if successful in clinical trials, ACE Mg may be contraindicated in several patient populations.

**Ebselen (SPI-1005)**

Either as a single agent (Rybak et al., 2000) or in combination with allopurinol (Lynch et al., 2005a,b), ebselen demonstrated some preclinical efficacy in reducing cisplatin-induced ototoxicity. Conversely, Lorito et al., 2011 did not find significant cisplatin otoprotection with ebselen, so results are inconsistent. Ebselen was shown to prevent free radical stresses in cochlear explants, thus preventing the ROS damage and subsequent apoptotic death typically seen as a result of cisplatin treatment (Kim et al., 2009). Guinea pig studies have also demonstrated ebselen protection from gentamicin-induced ototoxicity, suggesting that protection may extend across multiple ototoxic agents (Takumida et al., 1999).

Two clinical trials to evaluate ebselen for ototoxicity protection are approaching recruitment and enrollment: a phase 2 study targeting platinum chemotherapy ototoxicity treatment (Kil, 2016a), and a phase 1/2 study for the prevention and treatment of aminoglycoside-induced ototoxicity (Kil, 2016b). Lynch & Kil (2009) previously published a Phase 1 safety study that demonstrated a good safety profile for ebselen in an NIHL population.
**N-acetylcysteine (NAC)**

While Bock et al first reported in 1983 that N-acetylcysteine (NAC) exacerbated aminoglycoside-induced hearing loss in the guinea pig model, NAC investigations conducted since then have demonstrated protection from aminoglycoside-induced ototoxicity in several human studies (Kocyigit, 2011; Tokgoz et al., 2011). A systematic review with meta-analysis performed by Kranzer and colleagues summarized the evidence for the safety and otoprotective effect of NAC when co-administered with aminoglycosides and did support otoprotective effects, but with side effects of abdominal pain, nausea, vomiting, and diarrhea, and arthralgia increased 1.4-2.2 times (2015). The authors noted that further well-controlled clinical trials are needed. Transtympanic NAC has provided mixed results in two clinical trials to reduce cisplatin-induced ototoxicity: Yoo et al. (2014) found no statistically significant otoprotection, while Riga et al (2013) reported statistically significant protection but only for 8000 Hz using the patient’s opposite ear as a control.

**D-methionine (D-met)**

Thus far, D-methionine (D-met) has been in clinical trials for noise-induced and cisplatin-induced hearing loss and radiation-induced oral mucositis. A Phase 1 study was published showing a favorable safety profile (Hamstra et al., 2010). However, preclinical work has also demonstrated efficacy in protection from aminoglycoside-induced ototoxicity, where D-met protected against gentamicin-induced (Sha & Schacht, 2000), amikacin-induced (Campbell et al., 2007), tobramycin-induced (Fox et al., 2016), and
kanamycin-induced (Campbell et al., 2016) hearing loss without antimicrobial interference either in vitro or in vivo (Sha & Schacht 2000; Fox et al, 2016). Multiple pre-clinical studies have demonstrated D-met protection from cisplatin- and carboplatin-induced hearing loss (Campbell et al., 1996, 1999, 2007; Lockwood et al., 2000) as well as in one unpublished clinical trial (Campbell et al., 2009).

Cloven et al (2000) also showed no antitumor interference for cisplatin treatment from D-met. Nonetheless, to avoid risk of antitumor interference, D-met can be applied directly to the round window as a potential otoprotectant (Korver et al., 2002), although this application technique precludes possible protection of other systems such as the kidney or neural system.

**Coenzyme Q10**

Coenzyme Q10 is currently being tested in a clinical trial at the University of Antwerp in Belgium to determine its effects on tinnitus characteristics in patients with chronic tinnitus. However, two preclinical studies have suggested that coenzyme Q10 may also have efficacy in ameliorating drug-induced ototoxicity. Fetoni et al. (2012) demonstrated that Q-ter, a soluble formulation of coenzyme Q10, significantly reduced gentamicin-induced auditory evoked response threshold shift and prevented cochlear outer hair cell loss in albino guinea pigs. Astolfi et al. (2016) reported that a solution of coenzyme Q10 terclatrate and Acuval 400, a multivitamin supplement containing antioxidant agents
and minerals (Acu-Qter), prevented cisplatin-induced threshold shifts in rats. Thus, this agent may have potential to prevent or treat several auditory disorders.

*Alpha-lipoic acid*

Alpha-lipoic acid was first reported as a protective agent for aminoglycoside-induced ototoxicity by Conlon et al in 1999. Later reports confirmed otoprotection from cisplatin-induced (Rybak et al., 1999a & b) and carboplatin-induced (Husain et al., 2005) hearing loss in preclinical studies, and there is one completed clinical trial listed on ClinicalTrials.gov for protection against cisplatin (Martin, 2014). However, no clinical trial results for alpha lipoic acid and ototoxicity have been published.

*Sodium Thiosulfate*

A common antidote to cyanide poisoning, for decades sodium thiosulfate (STS) has also shown efficacy to protect against cisplatin-induced ototoxicity (Otto et al., 1988; Neuwelt et al, 1996). However STS is a cisplatin neutralizer (Jones et al., 1991; Church et al., 1995), thus it may diminish the cancer fighting properties of the chemotherapy. Several strategies have been employed in an attempt to use STS to reduce cisplatin-induced ototoxicity without reducing antitumor efficacy. Because STS is typically administered parenterally, injected through the blood stream either by intravenous or intra-arterial administration, and because STS has been shown to markedly interfere with cisplatin treatment efficacy, one clinical trial is currently investigating the efficacy of a local STS
application via trans-tympanic injections of a STS-hyaluronate gel prior to cisplatin treatments to prevent cisplatin-induced ototoxicity in head and neck cancer patients (Meyer, 2016). Another approach has been to delay the STS administration by several hours after the cisplatin administration in an attempt to allow tumor kill to first occur prior to administration for the later occurrence of ototoxicity (Muldoon et al., 2000; Harned et al, 2008). A Phase 3 study recently completed which investigated the effects of STS on cisplatin-induced hearing loss in a pediatric population (Clinicaltrials.gov NCT 00716976) (Freyer et al., 2017). Freyer et al. 2017 did report a significant reduction in cisplatin induced hearing loss but also a significant reduction in event free survival and overall survival in children with disseminated disease. For children with localized disease, event free survival and overall survival were reduced but not significantly. Several additional clinical trials for STS protection from cisplatin-induced ototoxicity are currently listed on ClinicalTrials.org.

Interestingly, STS has been tested for protection from noise-induced hearing loss (Pouyatos et al., 2007) and gentamicin-induced hearing loss (Hochman et al., 2006) and did not provide protection for either purpose in those studies.

*Ginko Biloba*

With a well-established safety profile and known antioxidant properties (Le Bars & Kastelan, 2000; McKenna et al., 2001), ginko biloba has been examined for prevention of hearing loss in animal model experiments and human trials (Cakil et al, 2012; Dias et
al., 2015; Dias, 2010; Huang et al., 2007; Finkler et al., 2012; Fukaya & Kanno, 1999; Ma et al., 2015). However, results have shown weak evidence of efficacy to date. Coupled with results from Miman and colleagues (2002) that ginko biloba may actually potentiate aminoglycoside-induced ototoxicity, further controlled trials are warranted before it can be considered as a viable over-the-counter recommendation.

Other Approaches:

Amifostine

Multiple clinical trials have been conducted using amifostine, a potent free-radical scavenger, to prevent cisplatin-induced ototoxicity but they have not demonstrated significant protection or reduction of cisplatin-induced hearing loss, including conducting a meta-analysis across multiple clinical trials (Duval & Daniel, 2012). Currently, amifostine is not recommended for either otoprotection or neuroprotection by the American Society of Clinical Oncology 2008 Clinical Practice Guideline Update Use of Chemotherapy and Radiation Therapy Protectants (Hensley et al., 2009). However efficacy of 251mifostine is included in one active clinical trial as a secondary endpoint on ClinicalTrials.gov without results available (ClinicalTrials.gov Identifier: NCT00003269).

Steroids

Steroids are commonly used for the treatment of several inner ear diseases and injuries. Dexamethasone and methylprednisolone, with known anti-ROS activity including
the ability to increase inherent cochlear ROS defenses, have been explored in animal models as protective agents to reduce cisplatin-induced ototoxicity. These steroids have successfully demonstrated potential therapeutic benefits through both histological and functional measures, though intra-tympanic delivery seemed to deliver better results than systemic administration (Özel et al., 2016; Waissbluth et al., 2012; Sun et al., 2016). Only one human study (Phase 4) was found in which 34 patients were recruited to receive 0.7ml of Dexamethasone Phosphate, 10mg/ml, injected unilaterally to the middle ear to prevent ototoxicity (Marshak et al., 2014). While only 15 subjects completed the trial due to morbidity or change in chemotherapy regimen, there was an apparent protective effect on hearing. Specifically, less hearing loss and outer hair cell dysfunction were observed in the treated group compared to controls (Marshak, 2015). Effect sizes from this trial were mild, and while additional studies have been conducted in NIHL, further controlled trials are needed across steroids, delivery methods, and patient populations for ototoxicity.

Pantoprazole:

An ongoing clinical trial at the Children's Hospital of Philadelphia is investigating Pantoprazole, a proton pump inhibitor (PPI) (Balis, 2016). The study is entitled “Pilot Study to Prevent Nephrotoxicity of High-Dose Methotrexate by Prolonging the Infusion Duration and Prevent Nephrotoxicity and Ototoxicity of Cisplatin With Pantoprazole in Children, Adolescents and Young Adults With Osteosarcoma” (ClinicalTrials.gov identifier: NCT01848457). No results are yet posted. However bench research has
suggested that pantoprazole may sensitize tumor cells to cisplatin treatment perhaps reducing the amount of cisplatin required for treatment (Huang et al, 2013; Luciani et al, 2004). Therefore, one method of reducing ototoxicity may be reducing the level of the ototoxin while retaining efficacy, rather than modifying the mechanism of ototoxic action directly.

Discussion & Conclusions

The number of agents in or approaching clinical trials for drug-induced ototoxicity is encouraging. The Food and Drug Administration (FDA) drug approval process is necessarily careful, expensive, and arduous. However, promising pre-clinical and clinical trials suggest one or more effective otoprotective agents will receive FDA-approval for clinical use in the not-too-distant future. Moreover, many of the current test agents protect against both chemotherapy- and aminoglycoside-induced hearing loss in preclinical studies, some with data demonstrating full retention of therapeutic efficacy.

Drug development pipelines for the prevention or treatment of medicine-induced ototoxic hearing loss must be considered in relation to several important factors, including: a) the primary condition for which the patient is being treated; b) the interactions ototoxicity-mediating drugs may have on those conditions and/or treatments; c) population characteristics (i.e., age or sex); d) delivery methods required to reach full efficacy potential for the proposed mechanism of action; and e) FDA requirements for approval. For the latter, it is important to understand the differences between an exempt (i.e.,
nutraceutical agents available at health food stores) versus over-the-counter versus prescription-only designation, and what that means to patients and their interdisciplinary care teams, as well as the sort of education and communication about those products that may need to be addressed.

Retention of hearing during and after a life threatening illness is a major quality of life issue for patients receiving these ototoxic drugs and their families. Communication impediment during and after a major lifetime stress like illness can delay progress of treatment and recovery. The goal of patient care is always to extend life duration but also to retain full life capabilities and enjoyment. Certainly hearing is a major factor of the latter, and the agents discussed herein, while not mature enough at this point, offer great promise toward that goal.
Chapter 6: Conclusions

This chapter will summarize the main ideas of this project and the program in which it was developed; namely, the translational science approach to strategic scientific progress. The innovation and significance of this work is addressed as well as the next steps for the PIHL group initiative as a whole.
6.1 **TRANSLATIONAL SCIENCE**

Translational Science (TS) has traditionally been conceived of in very linear terms where ideas are taken from the “bench” of basic science laboratories and shepherded through clinical research into a product to improve human health at the “bedside” of medical care. But the current understanding of TS has evolved to account for the multi-faceted and interdisciplinary environment, looking more like a matrix than a linear progression. The TS matrix expands both the impetus driving scientific inquiry and the inputs to the trajectory which discoveries will follow. These expanded considerations include clinical relevance and interdisciplinary implications, ethical and cultural acceptability, program implementation logistics and limitations, public policy and economic evaluations. The matrix is rich with feedback loops, inputs and processes which seek to proactively and systematically identify and address elements along the pathway of scientific discovery-to-translation which best positions those efforts for success.

The NIH recognized these complexities when implementing the national initiative known as the Clinical and Translational Science Awards (CTSA). These awards are intended to leverage existing academic health center infrastructure to accomplish and coordinate the various elements of systematic translational science pathways. An additional loop in the TS matrix is the continuing education and practice of professionals within health sciences fields to grow the TS model and adoption. As such, through the CTSA program at the University of Texas Health Science Center San Antonio (UTHSCSA), in coordination with the University of Texas at Austin (UT), and the
University of Texas at San Antonio (UTSA), a Ph.D. program was initiated to address core competencies within discovery, development, application, and implementation activities to more efficiently move “knowledge bi-directionally between basic research, clinical research, and applications to improve health outcomes in individuals and the community.” TS can be thought of in two simple terms: the “bench” laboratory and “bedside” clinical research activities (T1), and the research which promotes best practices, implementation success and policy development to most effectively direct, drive and translate those outcomes (T2) (Woolf, 2008).

This dissertation project falls along the T2 spectrum as a novel approach to translational science management including the development of both a solid evidence-base and comprehensive implementation framework to optimize adoption of best practices in research methodology. PIHL scientists have no defined standards to guide study design. Instead, they must rely on individual review of existing articles and their own best judgment. The lack of homogeneous study designs result in incomparable study outcomes difficult to interpret, and, in turn, delays in our ability to understand and progress the state of the science. The systematic review in this thesis did not focus on traditional safety or efficacy outcomes of specific pharmaceutical compounds, but instead sought to identify, characterize, evaluate, and correlate the methodological variables across the full translational spectrum of PIHL studies in order to generate the evidence-base needed to develop PIHL research design recommendations and guidance. The outcomes of this systematic review have the potential to create a roadmap for PIHL research design,
optimized for comparable outcomes, with future analysis of the database. More broadly, if successful, this project should translate to a “roadmap for roadmapping” across scientific disciplines, shifting the way scientists understand, conceive and organize “best study design practices,” thus providing a novel tool for optimizing the conduct of bench-to-bedside research.

6.2 SIGNIFICANCE

Members of the PIHL Group have reported that their technologies are being granted “breakthrough status” with the FDA. The field of PIHL research is an entirely open frontier for scientists and entrepreneurs alike. Moreover, hearing loss is a global public health concern (World Health Organization, 2015), and particularly pressing for DoD and VA solutions given the extraordinarily high prevalence in these respective populations (Veterans Benefits Administration, 2015; Department of Defense Hearing Center of Excellence, 2016). The translational science approach forces a simple question upon all investigators from bench to bedside: What is the impact of this work? In the case of this thesis, the answer is layered: 1) the impact of hearing loss on society is extremely high (e.g., high costs associated with treatment for millions of cases of hearing loss (Cooper et

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4 Breakthrough status is a designation “designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)” and is reserved for, as the name implies, novel therapies (U.S. Food and Drug Administration, 2014).
al., 2015), disability costs to the taxpayer for Veteran hearing loss (Veterans Benefits Administration, 2015), quality of life deterioration and correlated comorbidities of hearing loss (Lin, 2011 & 2012; Mick et al., 2014), etc.; 2) the need for a breakthrough drug for hearing loss has been acknowledged by the FDA (determined in PIHL group discussion); 3) current research outcomes are incomparable and disparate, and stakeholders (including gatekeepers in funding, regulatory, and publication lanes) have been primed to make necessary changes. The efforts described in this thesis are the result of requirements identified through consensus by leading experts in the PIHL field. The real impacts of this work will be realized when the question – “What is the impact of this work?” – is applied to all PIHL studies in their conceptual phase, using strategic and systematic quality and design standards. The bench PIHL scientist can ask, “Will my study design yield results valuable to the field?” and they will be armed with guidance to answer that question; not to dictate how to conduct discovery science, but to move PIHL research into the translational mindset.

6.3 INNOVATION

This thesis proposed an approach to develop and execute a translational plan for enhanced scientific progress using a novel systematic review evidence base. This approach will contribute not only to PIHL research but to the overall understanding, utilization and progression of translational science as an applied field. To be sure, this is not the first attempt to review auditory research methods, coming on the heels of efforts by the James Lind Alliance to establish core methods for tinnitus-related research (Hall et al., 2016); nor
is it the first to think of the value of systematic review beyond the confines of RCT synthesis. There are emerging efforts to apply transparent, systematic reviews in qualitative and mixed methods research common to health services research; here, too, quality and minimum standards for reporting are of central concern (Wong et al., 2013; Pluye et al., 2016). There is a growing interest in “Realist” methods for systematic review, focused on elements of interest across studies which the traditional methods of Cochrane systematic review and meta-analysis cannot address. The RAMESES Project – “Realist And MEta-narrative Evidence Syntheses: Evolving Standards” – an international voice for this aim, is currently working to produce publication standards for realist systematic reviews, much like the Cochrane Methodology group discussed above (http://www.ramesesproject.org). The three core focus areas listed on the website’s “Standards and Training materials” page are publication standards, methodological guidance, and training materials. While the contribution to grow the application of systematic review methods across disciplines and aims is warranted and welcome, the focus clearly remains training investigators how to conduct these reviews. Hopefully in time, both Cochrane and RAMESES will eventually move beyond this internal focus and take on methods to evaluate study methods in these disciplines as well.

As called for on the global, national, and discipline-specific stages, PIHL research is now working at the front edge of the movement to develop and improve research through standards, guidance, and toolkits produced by consensus in the PIHL group and, in the next BPRs, backed by evidence with the review presented here. Whether reviewing RCTs or
qualitative health services research, the methods developed here could serve as a model for methods assessments across all disciplines of research. Domains central to PIHL research – Species, Injury Exposures (Noise or Ototoxins), Measures, Intervention/Drug – which were used in this review, could all accept replacements specific to the concerns of other disciplines. This model also adapts principles of international quality standards to develop BRP guidances for all stakeholders of PIHL research. Just as PRISMA, CONSORT, ARRIVE and RAMESES Project developed trusted quality standards for both investigators and funders of research, so too, the PIHL group will develop the first set of quality standards for its own discipline which launch outcomes forward toward into a comparable and reproducible plane.

But reviews and standards are not enough. Information overload, interdisciplinary sprawl, scientific literacy, and political winds all present challenges to affecting actual change across diverse PIHL stakeholders (Manson, 2016). The time and scientific understanding required for becoming aware and staying abreast of current BRPs is a well-recognized problem for clinicians in the context of EBPs (Thorne, 2003). Pressure to spend time seeing patients is often not a competing concern for the bench scientist, but work overload is not unique to clinicians and thus scientists, too, often struggle to find time for browsing new literature outside of targeted searches. So the question of how to package BRPs in a trusted, easy to locate, access, and apply way is an important one to address. Just as evidence presented in RCTs, or the outcomes of Cochrane reviews of them, require good implementation strategies to translate into clinical practice, so too, reviews of study
methods will require an accompanying implementation strategy comparable to that provided by the PIHL group platform and operational model as well as the comprehensive dissemination pathway strategy described above.

6.4 Future Work

6.4.1 PIHL Group Directions

6.4.1.1 Evidence-based Best Research Practices

The information collected in the Aim 1 (systematic review) provides a rich foundation from which the PIHL group can continue to develop meaningful BRPs for the scientific community. There are many directions to head, and the committees within the PIHL group are comprised of SMEs highly capable of addressing challenges in each head-on.

The questions surrounding quality in PIHL research reporting are perhaps a first order of business. If there is hope that BRPs for research design will someday lead to comparable outcomes, then investigators using those BRPs would need to also have adopted best practices in reporting. The good news is that these already exist with ARRIVE and CONSORT guidelines (Schulz et al., 2010; Kilkenny et al., 2010). Their adoption is the remaining challenge. The peer-review publication system is a difficult enforcer due to the fact that one’s peers, by definition, ought to be comparably cognizant of such guidelines as the general investigator pool. Journal-wide guidelines for both authors and reviewers
could help solve this, but ultimately the enforcement of adoption of good reporting quality comes down to each journal ethos and process. The PHIL group can certainly socialize and endorse the use of these guidelines through existing and future relationships with relevant journals, and can also lead by example, ensuring that all publications that go out of the PIHL group are reviewed internally to assure they meet these standards prior to journal submission.

There are other areas to pursue directly obvious in the data collected in Aim 1. As touched upon in Chapter 3, further investigation into the outcomes deemed comparable in subsets of studies with similar methods designs can be assessed for possible confounders in animal model sex, strain, or breed. Similarly, noise exposures can be evaluated to determine maximum TTS or PTS by type of exposure. Any of these investigations will be dependent upon the k of articles with comparable designs to allow adequate power for analysis.

Differences in the statistical approaches and the impact those variations have on reported outcomes is itself a useful task. The analytic reporting in the articles included in this systematic review was limited to general statements about statistical tests used and the level of detail provided (i.e., simple statements like “ANOVA tests were used” versus detailed descriptions of which tests were applied to which measures and how variables were treated) varied greatly but was most often quite simple. We know that 171 studies employed analysis of variance strategies (ANOVA tests), but how did they treat their variables? Did they average frequencies or perform individual assessments? Did they
measure both ears, and if so, did they treat them as independent data variables or averaged or best ear? Was the Bonferroni or other method applied for multiple comparisons or were individual positive results selected out for reporting? These questions are not comprehensively answered to a degree which would allow reproducibility in most cases but an in-depth assessment with biostatistical expertise and author follow-up inquiries could piece together a suitably evidence-base from which to produce BPRs in analytic plans for PIHL studies.

Development of BRPs within the PIHL group will take some time. This all-volunteer network will continue to prioritize questions of interest and execute new reports in digestible quantities. Early targets have been met, but the preparation of early documents made clear the challenges that come with the myriad of study designs used in both pre-clinical and clinical investigations, directly stimulating this systematic review. The next targets have already been determined by the committees. These include:

- Development of a drug delivery matrix which characterizes delivery routes of administration by dosages (quantity), time points, administrator skill levels, location/method of delivery, documented drugs, optimal conditions for delivery, pros/cons/risks of each delivery and suggested end-users.
- Develop sound exposure matrix (for both humans and animals) which takes all elements of the data collected in Aim 1 and condenses down guidance for expected noise damage to ensure safe research practices.
- Both Human and Animal model outcome domains and instruments matrix which can develop a common understanding for what tools measure which aspects of therapeutic benefit or harm and how they expect to correlate to their higher- or lower-order species correlates; or whether there is no species-dependency at all.
- Minimum statistical analysis to achieve comparability in reported outcomes.
Another area ripe for the PIHL group is working to optimize inter-disciplinary representation in study teams. Where isolated otologists or physiologists may not have had access to highly skilled audiometric-focused biostatisticians or toxicologists, the PIHL group’s heterogeneous roster can supplement these deficits and offer opportunities to build well-rounded teams. Of the 25 studies with genetic measures included in Aim 1, only 2 of them included authors affiliated with genetic research-focused institutions, and only 11 studies overall included an author with a specific affiliation to a statistics-focused institution or department. These are observations based on author-reported affiliation, however, and may not reflect actual expertise of the authors involved but it does present a useful point of conversation and consideration for PIHL Group members and meetings. Moreover, while it is unreasonable to imagine every PIHL study incorporating an expert from every relevant field on every study team, the inherently interdisciplinary nature of PIHL studies would presumably benefit from more robust study teams with at least consulted expertise across all six primary domains, and specialty expertise as required for specialized measures or exposures, including genetic testing. Clinical trials in particular can be a mysterious endeavor to a life-long bench researcher who is attempting to translate a technology. Inputs by ENT, audiology, public health, biostatistics, and acoustic science professionals can be the difference between a well-designed clinical trial plan and a waste of time and undue risk to human populations.
6.4.1.2 Beyond the Noise

As new frontiers in PIHL research continue to develop and gain successes in the laboratory, they will have a place in the PIHL group for discussion and coordination as deemed necessary. While ototoxicity and regeneration were excluded from Aim 1 herein, they are both prime targets for the next application of this model. Ototoxicity already has a wealth of literature so massive that it dwarfs the return for NIHL publications. An effort to replicate this systematic review model for ototoxicity-focused PIHL research may not be practical without dedicated resources. But the current trajectory of the PIHL Ototoxicity committee may not require such a detailed systematic review to determine best practices. The PIHL group defined multiple areas where a review was indeed required for NIHL otoprotection study designs but has yet to define such territory for ototoxicity otoprotection. If it is warranted, the same database and process are adaptable to that cause.

For regeneration research, far less research has been conducted to date and thus a next project in that field may be relatively quick to accomplish and stand ready at the forefront of that scientific quest (see reviews in Fraco & Malgrange, 2017, Revuelta et al, 2017 or Zheng & Zuo, 2016 for more perspective). Due to the broad applicability that a successful regenerative product will have to the general public, potentially across multiple causes of hearing loss, it is a rapidly evolving field with many competing interests. This elevates already proprietary-sensitive discussions to higher levels of confidentiality and competitiveness and thus may pose new challenges to the PIHL group model. However, to date, the PIHL group has successfully integrated several
investigators from this field into the fold. The mutual benefits of PIHL participation are a promise for this group too – exposure to lessons learned from missteps and successes from the NIHL-targeted PIHL investigators can equate to time savings in the long run – and many are the same people, evolving in their careers to investigate new targets and indications.

Development of a PIHL Regeneration Database offers an interesting opportunity – to develop the first-ever prospective study design methods collection. Following the path of NIH’s eReporter, grants.gov, and ever-growing crowd-sourcing platforms, the PIHL group could move to a method where members are asked to fill in their own database entry for their studies. This method would ensure more accurate and comprehensive entry, avoiding transcription or translation bias of the data extractor since it would be provided straight from the source. It also avoids the need to find a dedicated resource to conduct retrospective data extraction as well. The average article entry time requirement in Aim 1 was roughly 2 hours. Most of that time was spent attempting to find critical pieces of information or interpret and translate reported elements into the database scheme. Asking an investigator to enter these same pieces of information about their own work, with which they are intimately familiar, ought to take no more than 20-30 minutes. If successful, the same could be attempted with the broad scale of ototoxocity research since dedicated resources to retrospectively populate such a database are unlikely.
6.4.2 Coalitions with policy and funding gatekeepers

The PIHL Group operating through the DoD HCE has offered great visibility and opportunity to collaborate with stakeholders at the highest levels in government, both in the U.S. and abroad. HCE and PIHL group advocacy for the importance of hearing and PIHL research to the DoD resulted in fruitful alliances with the DoD Medical Research and Materiel Command (MRMC)’s Advanced Development office. MRMC’s Research & Development (R&D) programs have a vested interest in PIHL research and have used outreach through the PIHL group to request inputs toward their own acquisition planning strategies through “Request for Information,” or RFI, dissemination and collection. The results of those efforts have the potential to create new program focus areas on PIHL research.

As such, the products of the PIHL Group will continue to inform the DoD, as well as the NIH’s National Institute on Deafness and Communication Disorders (NIDCD), and the VA. While it may seem obvious, given the large problem hearing loss is among the Veteran population, that the VA would be a primary sponsor of PIHL studies, it may actually come as a surprise to learn that the the VA portfolio funded only 3 of the studies included in this systematic review. However, the VA tends to focus more on health services research – the second half of the translational science spectrum or “T2” research which focuses on effectiveness in population health, implementation, etc., rather than on bench research. Thus, PIHL research is likely to grow on the radar of VA funding portfolio managers as technologies develop more robustly into the stage of clinical trials.
For the funding portfolio managers eager to fund sound science, for FDA reviewers seeking to approve products tested through reliable and reproducible research methods, and for investigators striving every day to reach the next breakthrough in hearing research, and PIHL research in particular, the PIHL group, armed with this evidence base, will continue to tackle the tough questions and put out evidence-based guidance. Through these continual refinements in research methods, the Warriors who serve and Veterans who have served in militaries around the world, as well as the general public plagued by hearing loss, may find viable therapies sooner than they otherwise could have for hearing preservation, rescue, and even regeneration.
Appendices

APPENDIX A. PIHL CHARTER

Charter for the
DOD Hearing Center of Excellence
Pharmaceutical Interventions for Hearing Loss (PIHL) Advisory Board

1. INTRODUCTION:

The Veterans Affairs 2011 annual benefits report shows hearing loss and/or tinnitus [ringing or noises in the ears with no external signal] have been the most prevalent injuries since 1998. Currently, tinnitus is the number one diagnosed injury impacting Service members. In 2011, there were 147,850 new cases of hearing loss and tinnitus reported in Veterans. The standing total for disabilities of the auditory system for Veterans is 1,679,146, with approximately one million unique cases accumulated in the Gulf War/Global War on Terror era between 2001 and 2011. It is a significant problem that has been rising annually since 2001 in military and DoD noise-exposed civilian populations.

It is estimated that over 10 million Americans have noise-induced hearing loss (NIHL). Hearing protection devices (HPDs), while largely effective at preventing NIHL, are often worn incorrectly or not at all, by choice or by necessity to hear other critical sounds, such as enemy localization. Noise exposures in some work settings can exceed maximum capabilities of HPDs thus causing permanent hearing loss. Some noise exposures transmit sound and other vibrations, including blast waves, directly to the
cochlea through bone conduction. Certain drug exposures also can contribute to hearing loss, such as cisplatin and/or carboplatin commonly used for patients undergoing platinum-based chemotherapy. For injured soldiers, aminoglycoside antibiotics may also cause ototoxic hearing loss and possibly exacerbate NIHL. Even with regenerative medicine and research on the horizon, there currently is no capability to restore natural hearing ability once a permanent hearing loss has occurred. All of these issues demand an alternate solution to prevent and treat hearing loss to protect the inner ear systems.

Research to develop pharmacologic otoprotective agents to prevent, reduce or reverse recent onset noise- or drug-induced hearing loss has been ongoing for over more than several decades. Currently, several different mechanisms have been shown to contribute to metabolic, noise-induced cochlear injury. Among these are: (1) rapid depletion of glutathione (GSH), the cell’s key antioxidant defense, (2) damage to the mitochondrion resulting in reduced bioenergetics or biogenesis, (3) perturbations in cochlear blood flow and (4) neuronal damage from high levels of neurotransmitters called excitotoxicity.

It is assumed that by showering the cochlea with free radical scavengers (L-NAC, vitamins A, C, E, Magnesium, Ebselin, D-methionine, etc.) that the cochlea could either be protected from noise or be rescued from the effects of noise and it now seems clear that antioxidant treatment started hours or even days later could still lead to a reduction in permanent threshold shifts. It is also clear that much of the cochlear hair cell loss is being produced by the so-called death programs in the cell where these death programs, or apoptosis, are normal cellular functions protecting the organism against cancer, or
even used during development to reduce cell number. It has been shown that anti-apoptotic drugs can reduce NIHL through both otoprotection and otorescue. Thus, pharmacologic strategies for otoprotection, namely, making the cochlea more biologically resistant to acoustic injury or treating the acutely-injured cochlea through pharmacologic intervention, becomes possible, even plausible, rather than simple reliance on mechanical hearing protection.

First generation otoprotectants have typically been used clinically for other indications, occur naturally in foods, or are quickly broken down into other molecules used in cellular metabolism. As such, they are natural targets for animal studies with an eye to transition to clinical trials. A number of agents fall into this category including antioxidants and micronutrients such as D-methionine, Vitamins A, C, and E and minerals such as magnesium. Second generation agents such as Ebselen, AM-111 and SRC inhibitors have been shown to provide significant biologic protection given at much lower doses. There are other agents currently under study that are representative of this next generation of drugs. Some can be administered orally but others may not be suitable for oral administration. Side effects, toxicity and other aspects of drug development must be investigated before moving forward to human trials.

Across both generations, most formulations are currently pre-Investigational New Drug (IND) stage. Some do not fall under FDA oversight because they fall into the nutraceutical category and do not claim to treat a specific disorder and are potentially exempt from the IND requirement. Several agents are on the cusp of an IND, however,
and because the DoD will neither approve human subjects research nor pharmaceutical distribution of any compounds without an IND/NDA, the developers of all technologies will be forced into the IND process if they want to test within DoD populations or market toward DoD pharmacy acquisitions.

Research and marketing efforts of otoprotectants and otorescue agents within and to the DoD is clearly on the rise and while the need is clearly justified, the means are so disparate, incomparable, and unregulated that there is a clear gap in DoD strategy, consensus and oversight. The PIHL group will serve as the DoD voice for these issues, as a stable body which represents the needs of the DoD, the Service members and their family members as these technologies continue to evolve.

2. AUTHORITY:

Public Law 110-417 Duncan Hunter NDAA 2009 Section 721 reads:

– “Secretary of Defense shall establish within the DoD centers of excellence (COE) to include a COE focused on the prevention, diagnosis, mitigation, treatment and rehabilitation of hearing loss and auditory system injury.

– The Secretary shall ensure that the Center:

• Collaborates to the maximum extent practicable with the Secretary of Veterans Affairs, institutions of higher education, and other appropriate public and private entities (including international entities).
• Collaboratively develops a registry with bi-directional data exchange to identify and track incidence and care for hearing loss and auditory injury.
• Utilize registry data to encourage and facilitate the conduct of research, development of best practices, and clinical education.”
3. PURPOSE: This Charter establishes the DoD Pharmaceutical Interventions for Hearing Loss (PIHL) group. The PIHL group is an advisory group to the DoD HCE. The Executive Director of the HCE charges the PIHL group to:

- Review existing State of the Science
- Determine minimal acceptable level(s) of functional performance for any potential translational agents
- Develop and validate evidence-based laboratory, animal and clinical assessment protocol methodology guidelines
- Recommend appropriate standards and technologies

4. SCOPE: This document establishes the relationships of the PIHL group with the DoD HCE, other organizations and personnel associated with pharmaceutical research, management, acquisitions, requirements generation, funding, training, testing, sustainment, and modernization.

5. OBJECTIVES: The PIHL group will provide subject matter advice and coordination in the development of otoprotectant and/or otorescue pharmaceutical agent research methodology, efficacy standards and implantation practices across the DoD and throughout the acquisition lifecycle, including all R&D phases. Specific Goals include:

a. Determine and maintain the current and comprehensive understanding of the State of the Science.
b. Determine evidence-based laboratory and animal testing methodology standards, including model selections, for the conduct of all pre-clinical science in
otoprotectant or otorescue agent research, to which emerging clinical technologies will be held.

c. Provide military research study population coordination by compiling and maintaining a comprehensive registry of potential research study population cohorts within the DoD.

d. Address, validate, prioritize, and recommend capability-based requirements for technology transition to the DoD.

e. Develop and make recommendations for research methodology for DoD stakeholder implementation.

6. DELIVERABLES: The PIHL group will provide the following to HCE and stakeholders:

   a. Meeting Minutes
   b. Action Items
   c. Program Management Review (PMR) Brief Updates
   d. Recommendations for Pharmaceutical Interventions for Hearing Loss research and development

7. PARTICIPATING MEMBERSHIP: The PIHL group consists of both primary and advisory members. Primary members are voting members and are expected to attend all Steering Meetings, working group and committee meetings as relevant, or designate an alternate to attend. Primary membership will include technical and subject matter representatives from Departments / Services as deemed appropriate by existing voting members. Stakeholders in addition to participating membership will be invited to attend an biennially hosted PIHL Group Meeting.

8. ROLES AND RESPONSIBILITIES:
The Executive Committee of the HCE will appoint the chair of this PIHL AB for a minimum of 2 years. The HCE will provide staff responsible for hosting, facilitating, recording, and coordinating the meetings as well as publishing PIHL AB minutes via the Chair. Primary members will review and vote on recommendations made by the Board. Primary members assist the Chair with the status of current and future requirements and initiatives, and provide the HCE with insight to allow for the balancing of Warfighter, Medical Department, and research needs.

The Chairperson of PIHL group is accountable to the DoD HCE Executive Director. The Chairperson coordinates the activities of the Board.

All members will be required to adhere to and work in the spirit of all relevant Federal, DoD and service specific regulations. All members will be required to complete required CITI training modules as follows:

1. Biomedical Research Basic Course
2. Good Clinical Practices Course
3. GCP Course for Trials With Investigational Drugs (International/ ICH focus) Course

All members will be required to sign a disclosure of Conflict of Interest statement which will detail any financial interests they may have in any PIHL-relevant technologies, patents, or related business ventures.
9. OPERATING PROCEDURES: Primary members will achieve consensus as the method to support final decisions and agreements. Summary recommendation and counterpoints shall be recorded and made available as requested or recommended for distribution.

10. ADMINISTRATION: The Board will convene quarterly via teleconference, biennially in person, and as needed to coincide with key Planning, Programming, Budgeting, and Execution System (PPBES) and other events to integrate, amplify, and expand the complex requirements associated with supporting pharmaceutical R&D and acquisitions activities and the HCE. Agenda and read ahead material (as appropriate) will be distributed to all advisory board members prior to the meeting. Minutes will be distributed to both primary and advisory representatives within two weeks of each meeting. Additional meetings will be held as required.

The following administrative and reporting relationships will exist among the WG members and representatives from other offices involved in auditory research matters:

   a. Provide recommendations on strategic research plans and individual research requests to the HCE Executive Director.
   b. Provide a copy of all correspondence, reports, and meeting minutes to HCE Executive Director.
   c. Provide annual membership lists to the HCE Executive Director.
   d. Primary members are responsible for disseminating information to their services/communities.
11. CHARTER CHANGES: The charter will be reviewed annually or at the direction of the WG Chair. If this Charter is not reviewed during two consecutive review cycles (4 years), then the Charter will be considered void.

12. EFFECTIVE TIME FRAME: This charter is effective immediately and will be reviewed and updated biannually as required.

13. SIGNATURE

___________________________________  Dated: ______________________

Executive Director
DoD Hearing Center of Excellence
### B.1 2012 PIHL Symposium: Agenda

**HCE Pharmaceutical Interventions for Hearing Loss (PIHL) Advisory Board All-Hands Annual Meeting**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>1300</td>
<td>Welcome, Introductions and HCE Briefing</td>
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<tr>
<td></td>
<td>HCE Director (Dr. Mark Packer) &amp;/or Research Director (Dr. Doug Brungart)</td>
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<tr>
<td>1320</td>
<td><strong>PIHL Introduction</strong></td>
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<td></td>
<td>HCE Meeting Facilitator - Tanisha Hammill</td>
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<tr>
<td>1340</td>
<td><strong>Pre-Clinical State of the Science Overview</strong></td>
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<tr>
<td></td>
<td>History and Physiology (NIOSH) - Rick Davis</td>
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<td></td>
<td>Current Work Review (Pittsburgh) - Roger Hamernik</td>
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<tr>
<td>1445</td>
<td><strong>Break</strong></td>
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<tr>
<td>1500</td>
<td>Clinical Studies Overview</td>
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<tr>
<td></td>
<td>PH II Update - Speakers: Dr. Ron Jackson, CAPT Michael Hoffer, Kathleen Campbell, Colleen LePrell</td>
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<tr>
<td>1630</td>
<td>Open Floor Discussion and Updates for Other Completed Trials</td>
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<td>NLT 1700</td>
<td>Adjourn for the Day</td>
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**Day 2: Friday, August 24**

*Moderated Discussions*

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<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>800</td>
<td>DoD Functional Performance Requirements &amp; Feasibility Discussion</td>
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<td></td>
<td>Topics For Discussion: Stability, Protection Levels, Toxicity, Delivery</td>
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<td></td>
<td>Moderator - Dr. Douglas Brungart</td>
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<tr>
<td></td>
<td>Panelists: LTC Marjorie Grantham, Heather Fenzl, Kurt Yankaskas, Dr. Ronald Jackson</td>
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**Breakouts**

*The HCE will video record each session and will make the videos available online*

<table>
<thead>
<tr>
<th>Track</th>
<th>Moderator</th>
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<tbody>
<tr>
<td><strong>PRE-CLINICAL</strong></td>
<td><strong>Ron Jackson</strong></td>
</tr>
<tr>
<td><strong>CLINICAL</strong></td>
<td><strong>Tanisha Hammill</strong></td>
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279
<table>
<thead>
<tr>
<th>Time</th>
<th>PRE-Clinical Track</th>
<th>Clinical Track</th>
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</table>
| 900  | **Goals for Systematic State of the Science Review**  
*Speaker: Rick Davis* | **DoD Study Populations**  
*Panelists: CPT Rebecca Ludwig, LT1 Virginia Bailey, LTC Kristen Casto, Kathy Cupp, Martin Slade, Thomas Helfer* |
| 930  | **Current Population Portfolio Efforts**  
*Speaker: Tanisha Hammill* | **Translation to Humans**  
*Speaker: CDR Royce Clifford*  
**Noise Exposures/Incidence of Injury**  
*Speakers: Kurt Yankaskas, Thomas Helfer* |
| 1000 | **Testing Methodologies: Addressing Variables with Standardization as the Goal** | **Statistical Power Assumptions**  
*Speaker: Martin Slade*  
**Animal Models**  
*Panelists: Lovelace representative, Sharon Kujawa, Roger Hamernik, Carey Balaban*  
**Logistics: Access, Line Leadership, CRADAs & Contracts, Oh My!**  
*Panel: Tanisha Hammill, Kathy Cupp, Kathy Campbell* |
| 1040 | **Break** | |
| 1100 | **Testing Methodologies (cont.):** | **Pharmaceutical Development in the DoD**  
*Speaker: Dr. Yung-Sung Cheng* |
### Appendix B.1 2012 PIHL Symposium: Agenda (continued)

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Panelists/Speakers</th>
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<tbody>
<tr>
<td>1130</td>
<td><strong>Noise Exposures</strong> (duration, frequency, type/source of noise, blast); Tests (ABRs, gap/no-gap, etc.)</td>
<td><em>Panelists: Kurt Yankaskas, LTC Marjorie Grantham, Thomas Helfer</em></td>
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<tr>
<td>1200</td>
<td><strong>Pharmaceutical Development:</strong> The FDA/IND Process</td>
<td><em>Speaker: Dr. Eric Basting</em></td>
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<td>1200</td>
<td>LUNCH</td>
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<tr>
<td>1300</td>
<td><strong>Delivery Methods</strong></td>
<td><em>Panelists: Rick Rogers, Ron Jackson, Ben Shapiro</em></td>
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<td></td>
<td><strong>Study Measurements</strong></td>
<td><em>Panelists: Dr. Eric Basting, Jonathan Kil, Kathleen Campbell, Kathy Cupp, Patrick Feeney, Lynne Marshall, Martin Slade, Rick Rogers, Sharon Kujawa</em></td>
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<td><em>Data Collection: Audiograms, DPOAEs, DNA, Blood, Saliva, Imaging</em></td>
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<td>1340</td>
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<td><em>PTS vs TTS: Feasibility of Testing Out</em></td>
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<td>1400</td>
<td><strong>Break</strong></td>
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<td></td>
<td><strong>Group Discussions</strong></td>
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<tr>
<td>1415</td>
<td><strong>Funding Overview:</strong> CDMRP, ONR, NIDCD, VA</td>
<td><em>Speakers: Tanisha Hammill, Kurt Yankaskas, Chris Moore, Gordon Hughes (&gt;20 min ea)</em></td>
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<tr>
<td>1545</td>
<td><strong>Project Topics and Considerations</strong></td>
<td>Benefits of Large-Scale Collaborative Efforts Genomic Data Capture Opportunities for Collaboration</td>
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### 2014 Symposium: Agenda

**HCE Pharmaceutical Interventions for Hearing Loss (PIHL)**

**Working Group All-Hands Biennial Meeting**

*Hosted by Office of Naval Research Noise Induced Hearing Loss Program*

*Doubletree By Hilton Hotel Annapolis, MD*

*August 7, 2014*

<table>
<thead>
<tr>
<th>Presenter</th>
<th>Subject</th>
<th>Start Time</th>
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<tbody>
<tr>
<td>Col Packer</td>
<td>Welcome, Intros and HCE briefing</td>
<td>8:00 AM</td>
<td>30</td>
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<td>D Brungart</td>
<td>PIHL Introduction and Direction</td>
<td>8:30 AM</td>
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<tr>
<td>T Hammill</td>
<td>Overview of Working Group to Date &amp; Guidance for Researchers: Overview Dissemination Plan</td>
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<td></td>
<td><strong>30 MINUTE BREAK</strong></td>
<td>9:30 AM</td>
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<tr>
<td>1a. Kil</td>
<td>Research Guidance Topics: (1.5 min each)</td>
<td>10:00 AM</td>
<td>120</td>
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<tr>
<td>1b. Campbell</td>
<td>1. Temporary and Permanent Threshold Shift.</td>
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<td>2. Slade</td>
<td>a. Alternate definitions for PTS and TTS</td>
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<td>4. LePrell</td>
<td>2. Statistical Considerations</td>
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<td>5. Clifford</td>
<td>3. Otoacoustic Emissions</td>
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<td>6. Haase</td>
<td>4. Supra-threshold Metrics (incl SIN)</td>
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<td>7. Feeney (for Henry)</td>
<td>5. Genetic Considerations</td>
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<td>7. Tinnitus Measurement</td>
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<td>8. DOD Requirements for Pharmaceutical Acquisition</td>
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<td></td>
<td><strong>60 MINUTE LUNCH BREAK</strong></td>
<td>12:00 PM</td>
<td>60</td>
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<tr>
<td>9. Murphy (for Davis)</td>
<td>Topics (con’t):</td>
<td>1:00 PM</td>
<td>90</td>
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<tr>
<td>10. Murphy (for Davis)</td>
<td>9. Impulsive Noise</td>
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<tr>
<td>11. Clavier</td>
<td>10. 24 hour damage risk criterion</td>
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<td>14. Sound measurements: industrial hygiene vs noise control</td>
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<tr>
<td>Kopke</td>
<td>Outcomes/Lessons Learned from Previous &amp; Current Clinical Trial PIs</td>
<td>2:30 PM</td>
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<tr>
<td>Campbell</td>
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<td>2:45 PM</td>
<td>15</td>
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<tr>
<td>LePrell</td>
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<td>3:00 PM</td>
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<tr>
<td>Kil</td>
<td></td>
<td>3:15 PM</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td><strong>30 MINUTE BREAK</strong></td>
<td>3:30 PM</td>
<td>30</td>
</tr>
<tr>
<td>Senchak</td>
<td>DOD Market Analysis: Epidemiology and Economic Burden of Hearing Loss</td>
<td>4:00 PM</td>
<td>45</td>
</tr>
<tr>
<td>Hammill</td>
<td>Summary and Next Steps</td>
<td>4:45 PM</td>
<td>45</td>
</tr>
</tbody>
</table>

**ADJOURN NLT**

5:30 PM
APPENDIX C. METHODS

C.1 SEARCH STRATEGY

The following is a PubMed-formatted version of the search strategy used.

2 (deaf[tiab] OR deafness[tiab] OR hearing loss[tiab])
3 #1 OR #2
5 (ear[tiab] OR cochlea*[tiab])
6 #4 OR #5
7 cell death[mesh:noexp] OR apoptosis/
8 (cell death[tiab] OR apopto*[tiab])
9 "Wounds AND Injuries"[mesh:noexp] OR (injury[tiab] OR trauma[tiab] OR damage[tiab])
10 #7 OR #8 OR #9
11 #6 AND #10
12 #3 OR #11
indomethacin OR indoprofen OR ketoprofen OR ketorolac tromethamine OR ketorolac OR meclofenamic acid OR mefenamic acid OR mesalamine OR methylprednisolone OR mometasone furoate OR naproxen OR nedocromil OR niflumic acid OR olopatazone hydrochloride OR oxyphenbutazone OR paramethasone OR phenylbutazone OR piroxicam OR prednisolone OR prednisone OR salicylate OR steroid OR sulfasalazine OR sulindac OR suprofen OR tilorone OR tolmetin OR triamcinolone OR 15 "24,25-dihydroxyvitamin d 3" OR "25-hydroxyvitamin d 2" OR acetylcarnitine OR acetylcysteine OR alpha-tocopherol OR ascorbic acid OR beta carotene OR beta-tocopherol OR biotin OR calcifiedol OR calcitriol OR carnitine OR cholecalciferol OR cobamides OR cod liver oil OR dehydroascorbic acid OR dihydrotachysterol OR dihydroxycholecalciferols OR ergocalciferols OR flavin mononucleotide OR folic acid OR formyltetrahydrofolates OR fursultiamin OR gamma-tocopherol OR hydroxocobalamin OR hydroxycholecalciferols OR inositol 1,4,5-trisphosphate OR inositol phosphates OR inositol OR magnesium OR niacin OR niacinamide OR nicorandil OR nicotinic acids OR palmitoylcarnitine OR palmitoyl carnitine OR panax notoginseng OR panax OR pantothenic acid OR phytic acid OR pteroylpolyglutamic acids OR pyridoxal phosphate OR pyridoxal OR pyridoxamine OR pyridoxine OR riboflavin OR superoxide dismutase OR tetrahydrofolates OR thiamine monophosphate OR thiamine pyrophosphate OR thiamine triphosphate OR thiamine OR thioctic acid OR tocopherols OR tocotrienols OR tocotrienols OR vitamin a OR vitamin b 12 OR vitamin b 6 OR vitamin b complex OR vitamin d OR vitamin e OR vitamin k 1 OR vitamin k 2 OR vitamin k 3 OR vitamin k OR vitamin u OR vitamins OR xanthopterin OR
16 "24,25-dihydroxyvitamin d 3" OR "25-hydroxyvitamin d 2" OR ginseng OR acetylcarnitine OR acetylcysteine OR alpha-tocopherol OR anti-apoptotic OR ascorbic acid OR Astragaloside OR beta carotene OR beta-tocopherol OR biotin OR calcifediol OR calcitriol OR carnitine OR cholecalciferol OR


21 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20

22 #12 AND #21


OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])

26 models, animal[mesh:noexp] or animals[mesh:noexp] or (mice[tiab] or mouse[tiab] or rat*[tiab] or gerbil*[tiab] or chinchilla*[tiab] or pig*[tiab] or primate*[tiab] or dog*[tiab] or cat*[tiab])

27 #23 OR #24 OR #25 OR #26

28 #22 AND #27

29 #28 AND english[la]
C.2 CODEBOOK

CODING & DATA ENTRY RULES FOR PHARMACEUTICAL INTERVENTIONS FOR HEARING LOSS (PIHL) METHODS SYSTEMATIC REVIEW

GENERAL INSTRUCTIONS

1.1 Instructions for the coder

- Before you begin coding a manuscript, make sure that you have received a training session from the principal investigator (PI) on how to efficiently use this codebook and coding form.
- Keep the study aims for this SR with you while coding a manuscript.
- Manuscripts will be included only if they meet the criteria listed in Section 1.2.
- Discuss all disagreements with the PI on a weekly basis.
- If a manuscript is determined to be ineligible, email the manuscript title, author and date to PI along with a brief note about why the article is ineligible.

1.2 Eligibility criteria

- The study must have a primary target for intervention of noise-induced hearing loss or noise-induced, peripheral tinnitus.
  - Studies focused on other auditory conditions, including congenital deafness, presbycusis (age-related hearing loss), sudden sensorineural hearing loss, or Meniere's disease, are not eligible.
  - Likewise, studies focused on pathophysiology, etiology, diagnostic or delivery routes, or drugs to CAUSE hearing loss or tinnitus, without a qualifying (e.g., drug) intervention, are not eligible.
- The intervention must be a chemical agent and not a device or technique (i.e., acupuncture or devices such as hearing aids or middle- or inner-ear implants).
- Study must be original, prospective, cohort research (i.e., no reviews, case reports, retrospective, etc.).
- Study model must be in vivo.
- Studies targeting hearing regeneration are ineligible.

1.3 Coding Rules- Overall

- Code studies, NOT citations. If one citation discusses multiple studies.
  - If 1 study has been published in 3 citations, you will use only 1 coding form for that study.
  - If 2 studies have been explained in 1 citation, you will use 2 coding forms.
- For each study that is coded, enter information on the following levels; Citation (C); Study (S), Study-Animal (SA), or Study-Clinical (SC); Noise Exposure (NE)
or Ototoxic Exposure (OE); Drug (D); Intervention Arm (I); Measures (M); Analyses (A); Outcomes (O); Quality (Q)

- Either check the appropriate field, choose drop-down option or SPECIFY details based on instructions in the coding form.
- Enter “NR” for data not reported in the manuscript.
- Enter “NA” for any question not applicable to the study type (e.g., an animal question for a clinical study).
- If the coding field requires a number (n) to be entered and the manuscript only reports a percentage, then you must report and notate the percentage instead.

**INSTRUCTIONS TO CODE CITATION INFORMATION (C)**

C 1 Ref Works ID: Enter the Ref Works ID number.

C 2 Name of coder: Enter last name of coder.

C 3 Publication Date: Enter date the manuscript was published as “YYYYMMDD”. If no month or day are listed, use zeroes.


C 5 Author Field/Discipline: if reported only. NR is acceptable. If this is gleaned from affiliated institutions, add "(NR)" afterwards to denote that it was not explicitly reported.

C 6 Citation source(s) - primary lit search ("PLS"), ad hoc search ("AHS"), "other - [specify]"

C 7 Number of studies reported in this citation

**INSTRUCTIONS TO CODE STUDY (S) LEVEL**

S 1 Study ID: Enter 1 as the default, unless ≥2 studies.

S 2 Phase: Animal, PH 0, I, II, III, or IV (or combination of numerals for a PH I/II study, for example); or “NR-Human” if phase is not reported; or “NA-Human” if citation reports that study was not applicable to FDA IND phases.

S 3 Study design: Mark if the study was an animal or human study using the categories below. Observational study designs (cohort, case control or cross-sectional) should be
listed under other but are not expected to occur frequently, and will be ascertained using the STROBE definitions.
  o Animal Experiment - Randomized
  o Animal Experiment - Non-Randomized
  o Non-randomized clinical trial
  o RCT - parallel
  o RCT - cross-over
  o RCT - cluster
  o RCT - factorial
  o Observational
  o Other (specify):

S 4 Study Location– City, State/Province, Country: Specify where the study was conducted.

S 5 Study Setting: Describe the setting of the study in this open field. Prefer common terms below if applicable:
  - Laboratory
  - Clinical
  - Field - [specify, e.g., Military]
  - Other - [specify]

S 6 Sponsor: Enter which of the following sponsored the study:
  - Industry Sponsored
  - US Government - NIH
  - US Government - DoD
  - US Government - VA
  - US Government - Other
  - Government, Non-US
  - Non-Government Organization (NGO)
  - Other (Specify)

S 7 Study enrollment years: Specify the time frame in which the study enrolled participants/began experiments with start date and completion date if provided (in YYYYMMDD format) or NR or NA as appropriate.

S 8 Injury or Disease Target: use whatever condition(s) were targeted for intervention. NIHL or Tinnitus must be at least one reported or the study is ineligible. If an ototoxicity arm is also included, that should be reported as well.

S 9 Indication: use intervention indication(s) reported (prophylaxis or acute rescue only; regeneration is an excluded target).
S 10 Exclusion Criteria: open text description.

S 11 Sample Size at Baseline: enter the total study N (intervention and control groups combined)

S 12 Control or comparison group description: If hearing protection devices (HPDs) were used among controls as a monitored part of the study (by self-report or observed) be sure to check the appropriate box. Other interventions may include devices such as a hearing aid. Please be specific when listing such alternative comparison groups.

- no placebo, no HPDs
- no placebo, with HPDs
- placebo, no HPDs
- placebo, with HPDs
- Other intervention, non-chemical [specify]
- None

S 13 Gender (% male total)

S 14 Randomization/Allocation Scheme. See CONSORT (clinical trials) or ARRIVE (animal studies) for items to record as reported.

S 15 Blindedness. Report who was blinded, when (e.g., throughout entire study, until data analysis, etc.).

S 16 Other pertinent information

INSTRUCTIONS TO CODE STUDY LEVEL: ANIMAL (SA)

SA 1 Animal Model: open text box - write in the species

SA 2 Animal Strain: open text box – NA or NR are acceptable

SA 3 Maturation or Age of the Animals Used. Age may not be reported in a uniform format across the studies or be available in the format specified on the coding form. If it is possible to calculate this information from data tables in manuscript, coder will do this. Check the field and also enter appropriate value in all possible fields. If coder is unable to ascertain age in any of the pre-defined fields on the coding form, then enter NR.

SA 4 Animal Weight Unit
SA 5 Animal Weight Range(s)

SA 6 Other relevant information provided. Use this space to provide any other details provided in the manuscript regarding the animal model used including, but not limited to the source of animals, genetic modifications, genotype, etc. See ARRIVE checklist for considerations.

INSTRUCTIONS TO CODE STUDY LEVEL: CLINICAL TRIAL STUDIES (SC)

SC 1 Age Proxy: Enter Proxy for age reported (e.g., range, mean, mean & SD, median, categories, etc.)

SC 2 Age: Enter a whole number. If coder is unable to ascertain age in any of the pre-defined fields on the coding form, then use NR.

SC 3 Ethnicity: Ethnicity may not be reported in a uniform format across the studies or be available in the format specified on the coding form. If it is possible to calculate this information into a % from data/tables in manuscript, coder will do this. If coder is unable to ascertain ethnicity in any of the pre-defined fields on the coding form, then use NR.

SC 4 Race/ethnicity: Race/ Ethnicity may not be reported in a uniform format across the studies or be available in the format specified on the coding form. If it is possible to calculate this information into a % from data/tables in manuscript, coder will do this. If coder is unable to ascertain race/ethnicity in any of the pre-defined fields on the coding form, then use NR.

SC 5 Weight ranges/BMI if reported (Specify in open text)

SC 6 SES: Socioeconomic status may not be reported in a uniform format across the studies. Coder may use information for data-tables or text to describe it as explained in the manuscript e.g., education, income, SES categories, and/or if proxy for SES then specify. If coder is unable to ascertain SES, then state ‘not specified’.

INSTRUCTIONS TO CODE EXPOSURE LEVEL – NOISE AND/OR OTOTOXIC

NOTE: Exposures can be reported as noise or chemical/ototoxic insults or both. Exposures may differ by exposure arms. If so, duplicate the appropriate exposure sections below to capture PER ARM.

Noise Exposure (NE)
NE 1 Exposure ID (Default= 1)

NE 2 Noise Type Choose one per arm:
- Impulse
- Continuous Steady State
- Blast
- Octave Band
- Pure Tone/Broadband
- Kertotic (mixture of broadband and impulse)
- Mixed (real world recordings, music)
- Spectrally Profiled (white, pink, etc.)
- Filtered
- Long-term/occupational history
- Life exposures over time
- Other [specify]
- No Noise Exposure

NE 3 Noise Source: Describe the source of the noise. There may be great variability in how this is done. Record as much detail as is provided in the manuscript (e.g., speaker numbers, brands, arrays, or recording type).

NE 4 HPD Use: choose from options - "Yes", "No", "NR", "NA"

NE 5 kHz: check Yes or No to all options as reported for this arm only. Do not leave options blank. NR is acceptable for all.

NE 6 Sound Level Measurement Unit:
- Decibels (dB)
- Sound Pressure Level (SPL)
- Other [specify]
- NR

NE 7: Sound Level Measurement (Using whole numbers, per scale identified in EN 6)

NE 8 Duration Unit of Measure Choose one per arm:
- If continuous: "HH:MM", "# of days", "# of impulse events", "Other - [specify]
- If non-continuous: "HH:MM"
- If Impluse: "# of events"

NE 9: Duration: Using scale identified in EN 8
**Ototoxic Exposures (OE)**

OE 1 Exposure ID (Default= 1)

OE 2-5 : Provide details on name, type, purpose/indication and dose(s) of the ototoxic agent. Also provide any other description of ototoxic insult that was mentioned in the paper.
Example:
Dose (specify): 125 mg (weeks 1-4), 250 mg (remainder of treatment)
Schedule (specify): Once daily or once in 3 weeks
Duration (specify): For 2 weeks after chemotherapy or simultaneously during cycles 1-4 of chemotherapy
Other (specify): ESA dose was determined after blood count monitoring in week 2, or rules for titrating dose.

**INSTRUCTIONS TO CODE DRUG LEVEL (D)**

When any variant among D1-7 coding variables exists, you must complete a new D1-7. Number subsequent sections D 2.1-2.7, D3.1-3.7 and so on. Examples may include variant dosing schedules or routes of administration with the same drug.

D 1 Drug ID. Starting with “1”, sequential numbering of each Drug section coded. First section (must be at least 1) will be numbered 1 and each variable will be 1.1, 1.2, 1.3…1.7.

D 2 Drug Name (may be “placebo”)

D 3 Drug Description: Use descriptions provided or known. Further classification will be conducted post hoc.

D 4 Dose Specify, e.g., “125 mg (weeks 1-4), 250 mg (remainder of treatment)”
D 5 Schedule Specify, e.g., “Once daily for 3 weeks”
D 6 Mechanism of Administration Specify (e.g., injection, tablet, etc)
D 7 Site of Administration Specify (e.g., intratympanic, oral, etc.)

**INSTRUCTIONS TO CODE MEASURE LEVEL (M)**

M 1 Measure ID (Default=1)
**M 2 Measure description**: open field text. (e.g., Pure Tone Audiometry, DPOAE, etc.) If a questionnaire is used, name it “Questionnaire-Name”. E.g., Questionnaire-SF36.

**M 3 Time Measure Unit**: "Weeks", "Days", "Hours", "Other - [Specify]"

**M 4 Time(s) measured**: open field text, enter times of measurement taken in M3 units, or NR or NA. Include relevant information of measures taken in relation to NE(s), OE(s), or D(s) administration schedules.

**M 5 Use of Measure in Study** (e.g., sample description, primary/secondary outcome, covariate, moderator, mediator, correlate, dependent variable).

**M 6 Source of Measure** (e.g., make/model of audiometer used, paper vs. online survey, etc.)

**M 7 Reliability info** (e.g., test-retest, inter-rater, intra-rater, calibrations) *Note whether info is from this study or another study.

**M 8 Validity info** (Predictive, criterion, content, and/or other validity w/ psychometric info.) *Note whether info is from this study or another study.

**M 9 Other info explicitly provided**

**M 10 Coder observations** (e.g., similarity of control group pre- post-test scores indicates stability)

**M 11 kHz of test used if applicable** (i.e., pure tone audiometry)

**INSTRUCTIONS TO CODE INTERVENTION LEVEL (I)**

**NOTE**: The instructions below can be repeated for as many study therapeutic intervention arms as were used. Any variant in the categories below constitutes separate study arms. If an Arm provided in the coding sheet (e.g., I 3 or I 4) was not used in the study, list “NOT APPLICABLE” across all fields. Add new study arms as needed for studies with > 4 I arms.

**I 1 Intervention ID (Default=1)**

**I 2 Exposure ID** Ensure you use exactly the correct version across variables.

**I 3 Drug ID** Ensure you use exactly the correct version across variables.

**I 4 Measure ID** Ensure you use exactly the correct version across variables.

**I 5 Subject N enrolled/randomized to this Arm**

**I 6 Subject N analyzed in this Arm**

**INSTRUCTIONS TO CODE ANALYSES LEVEL (A)**
A 1 N of subjects analyzed
A 2 Primary Aims
A 3 Secondary Aims
A 4 Primary Statistical Tests

INSTRUCTIONS TO CODE OUTCOMES LEVEL (O)

O 1 Open Text: enter descriptions of outcomes, preferably as related to primary and secondary aims above.

INSTRUCTIONS TO CODE QUALITY LEVEL (Q, AND QA OR QC)
(FUTURE EFFORTS)

Q 1: Risk of Bias Assessment: Using Cochrane Risk of Bias tool, select High, Low, NA, or Unclear for each:
✓ Selection Bias
✓ Performance Bias
✓ Detection Bias
✓ Attrition Bias
✓ Reporting Bias
✓ Other Bias

QA = Quality for Animal Studies
QC = Quality for Clinical Studies
You will choose only one and mark “NA” for the other.

QA 1: Enter the total number of ARRIVE checklist items confirmed (of 20)
Using the instructions/descriptions on the ARRIVE Table checklist, check Yes, No, Partial, NA or NR for each:
✓ Title
✓ Abstract
✓ Background A
✓ Background B
✓ Objectives
✓ Ethical Statement
✓ Study Design A
✓ Study Design B
✓ Study Design C
✓ Experimental Procedures A
✓ Experimental Procedures B
QC 1: Enter the number of CONSORT checklist items confirmed (of 37)

Using the instructions/descriptions on the CONSORT Table checklist, check Yes, No, Partial, NA or NR for each:

Title/abstract Category:
- Yes Title
- Yes Abstract

Introduction Category:
- Yes Background
- Yes Objectives

Methods Category:
- Yes Trial design
- Yes Design changes
✓ Participants – eligibility
✓ Participants – Settings and location
✓ Interventions
✓ Outcomes- defined measures
✓ Outcomes- changes defined
✓ Sample size determination
✓ Sample size interim analysis or stopping guidance
✓ Randomization Sequence generation
✓ Randomization type
✓ Allocation concealment mechanism
✓ Implementation
✓ Blinding – who
✓ Blinding – difference among interventions
✓ Statistical methods – to compare groups for primary/secondary aims
✓ Statistical methods – for additional analyses

Results Category:
✓ Participant flow (a diagram is strongly recommended) - #s per group
✓ Participant flow – losses and exclusions
✓ Recruitment – periods of recruitment/follow-up
✓ Recruitment – why it stopped
✓ Baseline data tables
✓ Numbers analyzed
✓ Outcomes and estimation – primary/secondary
✓ Outcomes and estimation – effect sizes
✓ Ancillary analyses
✓ Harms

Discussion Category:
✓ Discussion
✓ Limitations
✓ Generalizability
✓ Interpretation
✓ Other information

Other Information Category:
✓ Registration
✓ Protocol
✓ Funding
### APPENDIX D. EVIDENCE TABLE, K=213

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<th>Region</th>
<th>Author Institutional Discipline</th>
<th>Journal</th>
<th>Species</th>
<th>Sample Size / Analyzed N</th>
<th>% Male Subjects</th>
<th>Indication</th>
<th>Drug(s)</th>
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<td>France</td>
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<td>Rescue</td>
<td>Magnesium Methylpredisolone</td>
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<td>Biomedical research, ENT</td>
<td>Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS)</td>
<td>guinea pig</td>
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<td>Furosemide</td>
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<td>Study</td>
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<td>Country</td>
<td>Field</td>
<td>Journal</td>
<td>Species</td>
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<td>Treatment Duration</td>
<td>Methodology</td>
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<td>Biochemical and Biophysical Research Communications</td>
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<td>Acta Oto-Laryngologica</td>
<td>guinea</td>
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<td>21 / 21</td>
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<td>Physiology and pharmacology</td>
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<td>21 / 21</td>
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<td>Otology &amp; Neurology</td>
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<td>320 / NR</td>
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<td>Country</td>
<td>Study Design</td>
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<td>Species</td>
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<td>Treatment</td>
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<td>46 / 46</td>
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<td>Neuroscience Research</td>
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<td>34 / 34</td>
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### Appendix D. Evidence Table (continued)

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## Appendix D. Evidence Table (continued)

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324
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APPENDIX E. PRESENTATIONS

Presentations delivered at national and international meetings to relevant stakeholders, promoting and disseminating PIHL messaging are included below. The cover slides depict where each slide set was presented.

E.1 AudiologyNOW! Annual conference, Orlando, FL, March 26-29, 2014

USAF disclaimer

The views expressed in this presentation are those of the author and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the U. S. Government.

MILITARY NOISE

- Military operations are inherently noisy
- Ability to hear and communicate is critical for mission performance

- Most Hearing loss can be mitigated
- Hearing disability costs are huge
...YES, NOISE IS A PROBLEM

HEARING LOSS IS A BIG PROBLEM

DoD-wide issue, leading to a VA issue

(Source: VA)

Annual VA Awards: $1 Billion
PPE/HPD LIMITATIONS

- All HPDs rely on
  - material to block sound waves
  - occlusion (seal)
  - appropriate use

- Currently at technologic limit for HPD of ~50-60 dB attenuation in noise environments up to 100 dB over the safe limit for an 8 hr period of exposure

- Weapons fire
  - 165-170 dB
- Jet Planes
  - 120-180 dB
- Grenades/Mortar
  - 165/185 dB

PHARMACEUTICAL SOLUTION: DRUG DEVELOPMENT

The Need

The Idea

The Approval

The Development

The Marketing
### Drug Development

- **Drug Discovery**: 6.5 yr
- **Drug Development**: 8.5 yr
- **Early research/Preclinical testing**: 1970
- **IND**: 5 yr
- **Ph I**: 5 yr
- **Ph II**: 5 yr
- **Ph III**: 5 yr
- **FDA Review**: 5 yr

### PIHL Development

- ✔ Compound(s) Identified and Readily Available
- ✔ Patentable/License ready
- ✔ Mass Application
- ✔ Marketable
PHARMACEUTICAL SOLUTION: DRUG DEVELOPMENT

The Need

The Idea (clinical/academia/laboratory)

The Development
Early: academia/labs
Later: biotech, investment capital firms
Final Stretch: Big Pharma

The Approval

The Marketing

GAP SUMMARY

- Hazardous noise is prevalent and pervasive in military environments
- Noise injuries are an epidemic in military populations
- Protective and preventative equipment solutions, while potentially highly effective, have limitations
- Pharmaceutical solutions have lingered on the horizon for decades, limited by:
  - targeted and translational funding,
  - efficacy translation from animal to human model,
  - Study populations and other FDA translation shortcomings
  - Lack of interest from Big Pharma
ADVISORY BOARD & WORKING GROUP STRUCTURE

- Chartered by the HCE’s Director in July 2012, the PIHL WG is overseen by:
  - Government Advisory Board, consisting of Tri-service representatives from:
    - HCE Hearing Health Program
    - ENT and Audiology providers
    - Pharmacy (designated by consultants)
    - Public Health
    - Data Management
  - Working Group: an open invitation membership forum consisting of leaders and subject matter experts from
    - The VA
    - NIH’s NIDCD, CDC’s NIOSH and other Federal agencies
    - Academia
    - Industry
    - International collaborators

PIHL CHARTER

The PIHL AB will provide subject matter advice and coordination in the development of ototoxicant and/or ototoxic pharmaceutical agent research methodology, efficacy standards and implantation practices across the DOD and throughout the acquisition lifecycle, including all R&D phases. Specific goals include:

a. Determine and maintain the current and comprehensive understanding of the State of the Science.

b. Determine evidence-based laboratory and animal testing methodology standards, including model selections, for the conduct of all pre-clinical science in ototoxicant or ototoxic agent research, to which emerging clinical technologies will be held.

c. Provide military research study population coordination by compiling and maintaining a comprehensive registry of potential research study population cohorts within the DOD.

d. Address, validate, prioritize, and recommend capability-based requirements for technology transition to the DOD.

e. Develop and make recommendations for research methodology for DOD stakeholder implementation.
# 1st "Annual" Meeting

**Pharmacological Intervention for Hearing Loss (PHIL) Advisory Board: 4th Annual Meeting**

**Day 2: Pharmacology**

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**Day 3: Preclinical, Clinical, NHE**

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<td>[Details]</td>
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<td>10:30</td>
<td>Clinical, NHE</td>
<td>[Details]</td>
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**Day 4: Preclinical, Clinical, NHE**

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**Committees Snapshot**

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<tr>
<th>Committee</th>
<th>PHIL Working Group</th>
<th>DOE Functional Requirements</th>
<th>TT5 vs TT5</th>
<th>Sound Exposures</th>
<th>Clinical Trial Testing Guidelines</th>
<th>Animal Models</th>
<th>Delivery Methods</th>
<th>Statistical Considerations</th>
<th>Generic Considerations</th>
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*Advisory Board Members:*
- [List of members with contact information]
CLINICAL TRIAL TESTING

• Primary Objectives:
  – To create written guidelines for clinical trials for otoprotective agents and devices to prevent noise-induced hearing loss:
    • Review of noise-notch and threshold changes observed with noise exposures in humans
    • Auditory threshold measurement for TTS and PTS
    • Statistical considerations and selection of primary and secondary outcome measures
  – Additional measures that may be considered for clinical trials:
    • Otoacoustic emissions
    • Word recognition, including speech in noise
    • Tinnitus measures
    • Biomarkers
    • Logistics of Data Collection within the DoD
    • Approval Processes for Clinical Trials within the DoD
  – Work with professional academies for community buy-in, awareness and adoption

DOD FUNCTIONAL REQUIREMENTS

Goals:
• To make pharmaceuticals more useful in combat situations
• Develop a DoD Functional Requirements to include:
  – Shelf life requirements
  – Dosing in theater
  – Storage temperature requirements
  – Optimal delivery routes per operational environment

• Planned outputs:
  – DOD PIHL guidance document for acquisition community
## DELIVERY METHODS MATRIX

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<th>Round window</th>
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<td># of Doses</td>
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<td>Flightdeck Treatment</td>
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<td>Timing of Delivery</td>
<td>a. pre- and post- blast exposure</td>
<td>b. physical: necrotic, traumatic</td>
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<td>Location of Delivery</td>
<td>a. in field, centrum</td>
<td>b. in clinic</td>
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<td>Optimal Conditions for Delivery</td>
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</tr>
<tr>
<td>Pen</td>
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<td>Prox</td>
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<tr>
<td>Suggested End User</td>
<td>a. Soldier in field, victim in clinic</td>
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## TTS/PTS

- Provide formal guidance, best practices, and/or publications on standards to define TTS and PTS
- Provide recommendations on TTS vs PTS as a primary outcome measure, along with secondary measures of outcome to consider
- Provide recommendations on further studies if needed

- Review State of the Science
- Monitor use of TTS in research
- Create Standards to define TTS and PTS injuries
- Define other outcome measures to consider
STATISTICAL CONSIDERATIONS

• Goal 1: State of the Science Review
• Goal 2: Creation of standardizations and/or guidance for statistical measures to be performed in studies regarding pharmaceutical interventions for noise-induced hearing loss
• Goal 3: As a part of Goal 2, create a minimal statistical battery for different types of studies
  • Necessary action - Determine types of studies:
    – Human
    – Animal
    – Longitudinal
    – Cross-sectional
    – Other types? Combinations?

GENOMICS

Still recruiting interested SMEs!
SOUND EXPOSURES

• Objective: To create frequency, duration and intensity sound exposure guidelines and recommendations for various animal and human testing
  – Focusing on exposure guidelines regarding safe exposure during noise research (esp. for human research)

• Action items:
  – Develop guidelines for human and animal noise testing
    • Develop guidelines for noise recordings
    • Create a compendium of noise exposure systems
    • Review state of the science
    • Create sound exposure guidelines
    • Assess and relate to Hearing Critical Tasks (conjunction with HCE FFD group)

ANIMAL MODELS

• Animal Model Matrix
  • Important strains
  • Availability of pigmented animals
  • Availability of SFF animals
  • Price range of animals
  • Husbandry cost price range
  • Lesion symmetry
  – Proposed Animal Models:
    • Chinchilla
    • Mouse
    • Guinea Pig
    • Rat
    • Gerbil
    • Canine
    • Marine Mammals
    • Non-Human Primate
    • Pig

• Quarterly Newsletter

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THE NEW SNAPSHOT

Committee:

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<th>PHIL Working Group</th>
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<th>Animal Committee</th>
<th>Sound Committee</th>
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<td>Charter Member Representative(s)</td>
<td>Mark Packer (CoI, USAF)</td>
<td>Vickie Tunton (COI, USA) &amp; James Crawford (ITC, USA)</td>
<td>Michael Neffor (CAPT, USN)</td>
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Administrative Lead/POC(s)

| Tanisha Hammill (tanisha.hammill.ctr@us.af.mil) | JR Stefanson (jw.stefanson.ctr@mail.mil); Kia Brooks (kia.l.brooks.ctr@health.mil); Kate Marshall (kathryn.e.marshall.ctr@us.army.mil); Kelly Watts (kfwatts@gmail.com); Elsa Camou (elsa.camo1.ctr@us.af.mil) | Sara Murphy (sara.murphy.ctr@med.navy.mil); Sarah Sullivan (sarah.sullivan.6.ctr@us.af.mil) |

REQUIREMENTS, ISSUES AND NEXT STEPS

- Volunteers – this effort has a small dedicated % effort from 9 HCE staff. All other participants (> 100) are volunteering their time.

- Travel approvals (dirty words!) – teleconferences have been successful but cannot replace the efficacy of in-person time, as evidenced by the massive coordination achieved in Baltimore and here this week!

- Big Pharma, Biotech and private investments industries outreach

- Publications, coming soon!
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E.2 San Antonio Military Health System & Universities Research Forum (SURF),
San Antonio, TX, June, 2015

HCE MISSION

- To heighten readiness and to continuously improve the health and quality of life for members of the Armed Forces and Veterans through advocacy and leadership in the development of initiatives focused on the prevention, diagnosis, mitigation, treatment, rehabilitation, and research of hearing loss and audio-vestibular system injuries.
- Date Established: 18 May 2010 with AF as Lead Component.
- Congressional Language: P.L. 110-417 Sec 721(a)
  - SECDEF shall establish, within the DoD, a center of excellence in the prevention, diagnosis, mitigation, treatment, and rehabilitation of hearing loss and auditory system injury.
  - Ensure collaboration... with VA/Academia/industry/International
  - Collaboratively develop a registry with bi-directional data exchange to identify and track incidence and care for hearing loss and auditory injury.
  - Utilize registry data to encourage and facilitate the conduct of research, development of best practices, and clinical education.
REGIONAL COORDINATION ACROSS THE HEARING AND BALANCE RESEARCH NETWORK

- Local site augmentation
- Knowledge management
- Deployment/transition of new technologies
- Multi-site coordination/centralized IRB
- Coordinated strategic planning
- Synergy of expertise

CAVRN

Collaborative Auditory/Vestibular Research Network (CAVRN) is a structured collaboration among all DOD and VA researchers from laboratories, medical treatment facilities (MTFs), Public Health Commands and peripheral Federal agencies with a focus in auditory research.

Scientific Steering
CAVRN informs the HCE Research Roadmap

Current Participant Roster: ~175
MILITARY NOISE

- Military operations are inherently noisy
- Ability to hear and communicate is critical for mission performance

- Most Hearing loss can be mitigated
- Hearing disability costs are huge
PPE/HPD LIMITATIONS

- All HPDs rely on
  - material to block sound waves
  - occlusion (seal)
  - appropriate use

- Currently at technologic limit for HPD of ~50-60 dB attenuation in noise environments up to 100 dB over the safe limit for an 8 hr period of exposure

- Weapons fire
  - 165-170 dB
- Jet Planes
  - 120-180 dB
- Grenades/Mortar
  - 165/185 dB

IT’S A NOISY WORLD AND A NOISIER MILITARY
**PIHL CHARTER**

Chartered by the HCE’s Director in July 2012:

The PIHL AB will provide subject matter advice and coordination in the development of ototoxic and/or otorescue pharmaceutical agent research methodology, efficacy standards and implantation practices across the DOD and throughout the acquisition lifecycle, including all R&D phases. Specific Goals include:

a. Determine and maintain the current and comprehensive understanding of the State of the Science.

b. Determine evidence-based laboratory and animal testing methodology standards, including model selections, for the conduct of all pre-clinical science in ototoxic and/or otorescue agent research, to which emerging clinical technologies will be held.

c. Provide military research study population coordination by compiling and maintaining a comprehensive registry of potential research study population cohorts within the DOD.

d. Address, validate, prioritize, and recommend capability-based requirements for technology transition to the DOD.

e. Develop and make recommendations for research methodology for DOD stakeholder implementation.

**1ST “ANNUAL” MEETING**

HCE: Pharmaceutical Interventions for Hearing Loss (PIHL)

Advisory Board AB Annual Meeting

<table>
<thead>
<tr>
<th>Time</th>
<th>Session 1</th>
<th>Session 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:00 PM</td>
<td>1. Introduction to the Session</td>
<td>1. Review of Prior Year’s Work</td>
</tr>
<tr>
<td>1:10 PM</td>
<td>2. Update on the State of the Science</td>
<td>2. Current Research Efforts</td>
</tr>
<tr>
<td>1:30 PM</td>
<td>3. Latest Publications and Research Highlights</td>
<td>3. Future Research Directions</td>
</tr>
<tr>
<td>1:50 PM</td>
<td>4. Q&amp;A</td>
<td>4. Panel Discussion</td>
</tr>
</tbody>
</table>

**AMERICA**

**Closing Remarks**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session 1</th>
<th>Session 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>5:00 PM</td>
<td>1. Summary of Key Points</td>
<td>1. Final Panel Statements</td>
</tr>
<tr>
<td>5:15 PM</td>
<td>2. Thank You</td>
<td>2. Adjournment</td>
</tr>
</tbody>
</table>
GAP SUMMARY

- Pharmaceutical solutions have lingered on the horizon for decades, limited by:
  - Efficacy translation from animal to human model
  - Study populations and other logistical issues
  - Targeted and translational funding,
  - Lack of interest from Big Pharma
  - Lack of unified guidance for investigations/investigators

PIHL COMMITTEES SNAPSHOT

PIHL Working Group Committees to address elements of research design and execution:
- Clinical Trials Guidance
  - Defining Outcomes: Temporary vs Permanent Threshold Shifts
  - Statistical Considerations
  - Genomic Considerations
  - DOD Functional Requirements

- Animal Research Guidance
  - Drug Deliver Methods

- Sound Exposures
CLINICAL TRIAL TESTING

• Primary Objectives:
  – To create written guidelines for clinical trials for otoprotective agents and devices to prevent noise-induced hearing loss:
    • Review of noise-notch and threshold changes observed with noise exposures in humans
    • Auditory threshold measurement for TTS and PTS
    • Statistical considerations and selection of primary and secondary outcome measures
  – Additional measures that may be considered for clinical trials:
    • Otoacoustic emissions
    • Word recognition, including speech in noise
    • Tinnitus measures
    • Biomarkers
    • Logistics of Data Collection within the DoD
    • Approval Processes for Clinical Trials within the DoD
  – Work with professional academies for community buy-in, awareness and adoption

DOD FUNCTIONAL REQUIREMENTS

Goals:
• To make pharmaceuticals more useful in combat situations
• Develop a DoD Functional Requirements to include:
  – Shelf life requirements
  – Dosing in theater
  – Storage temperature requirements
  – Optimal delivery routes per operational environment

• Planned outputs:
  – DOD PIHL guidance document for acquisition community
### DELIVERY METHODS MATRIX

<table>
<thead>
<tr>
<th>Delivery Method</th>
<th>Trans-synaptic</th>
<th>Intranasal</th>
<th>Auditory (if still under development)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of Device</td>
<td>Injection</td>
<td>Drops</td>
<td>Pumps, Deposit System, Solid Drug Cores, Drug Delivery (intrahepatic, intramuscular, intravenous, trans-oral, transcutaneous)</td>
</tr>
<tr>
<td>Dosage Amount</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of Uses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timing of Delivery</td>
<td>a, pre- and post- shock exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration of Delivery</td>
<td>a, physical, oral, nasal, rectal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location of Delivery</td>
<td>a, in field, in clinic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal Conditions for Delivery</td>
<td></td>
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<td>Pen</td>
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<td>###</td>
<td>###</td>
</tr>
<tr>
<td>Suggested End-User</td>
<td>a, Solid or in Field, Tissues or Clinic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TEMPORARY VS PERMANENT THRESHOLD SHIFT

- Provide formal guidance, best practices, and/or publications on standards to define TTS and PTS
- Provide recommendations on TTS vs PTS as a primary outcome measure, along with secondary measures of outcome to consider
- Provide recommendations on further studies if needed

- Review State of the Science
- Monitor use of TTS in research
- Create Standards to define TTS and PTS injuries
- Define other outcome measures to consider
STATISTICAL CONSIDERATIONS

- Goal 1: State of the Science Review
- Goal 2: Creation of standardizations and/or guidance for statistical measures to be performed in studies regarding pharmaceutical interventions for noise-induced hearing loss
- Goal 3: As a part of Goal 2, create a minimal statistical battery for different types of studies
  - Necessary action - Determine types of studies:
    - Human
    - Animal
    - Longitudinal
    - Cross-sectional
    - Other types? Combinations?

GENOMICS
SOUND EXPOSURES

• Objective: To create frequency, duration and intensity sound exposure guidelines and recommendations for various animal and human testing
  – Focusing on exposure guidelines regarding safe exposure during noise research (esp. for human research)

• Action items:
  – Develop guidelines for human and animal noise testing
    • Develop guidelines for noise recordings
    • Create a compendium of noise exposure systems
    • Review state of the science
    • Create sound exposure guidelines
    • Assess and relate to Hearing Critical Tasks (conjunction with HCE FFD group)

ANIMAL MODELS

• Animal Model Matrix
  • Important strains
  • Availability of pigmented animals
  • Availability of SFF animals
  • Price range of animals
  • Husbandry cost price range
  • Lesion symmetry
  – Proposed Animal Models:
    • Chinchilla
    • Mouse
    • Guinea Pig
    • Rat
    • Gerbil
    • Canine
    • Marine Mammals
    • Non-Human Primate
    • Pig
FOCUS AREAS EMERGED

- Test Methodology and metrics must be standardized and clinically valid endpoints established for future clinical studies
- Military requirements for pharmaceuticals for preventing and treating NIHL must be determined
- CONFERENCE PRESENTATIONS, NEWSLETTERS, WHITE PAPERS, PEER-REVIEWED PUBLICATIONS
- Study populations within the DOD are needed for clinical trials
- EPIDEMIOLOGY
- An Objective assessment/review of the studies and other data supporting the TRL 5 and above compounds is needed.
- STANDARDIZATION OF DATA ELEMENTS ➔ SYSTEMATIC REVIEWS
- A central repository of research-quality sound recordings.
- NOISE SOUND REPOSITORY

OUTCOMES

Three NEWSLETTERS are available online at hearing.health.mil with Vol. 4 expected in August. They rotate between themes of the primary committees and results of the work therein.

8 Clinical Trials Guidance (CTG) and 5 Sound Exposures WHITE PAPERS have been drafted and are included in their relevant Newsletter, available online.

The 8 CTG white papers were developed into full articles for peer review and currently pending approval for publication as a JOURNAL SPECIAL EDITION.

The currently contracted effort, "DOD Epidemiology and Economic Burden of Hearing Loss Study (DEEBHLS) is in its 9th and final year in collaboration with the UTSPH. Several publications have been accepted, are drafted or are planned for the upcoming year, including analysis which will identify vulnerable populations for research of PIHI agents.

As part of my own program as Translational Science PhD student at UTHSCSA/UTSA/UT-Austin and UTSPH, I will be conducting a SYSTEMATIC REVIEW over the next year to assess the methodologies employed to date across PIHI literature. Due to the heterogeneity of these methods, a meta-analysis of outcomes is not possible at this time.

The HCE launched NOISE SOUND REPOSITORY available to the public this last Spring at:

http://militarysounds.org/
NEXT STEPS

1. Commercialization Solutions
2. Clinical Trial Strategies

POTENTIAL COMMERCIALIZATION SOLUTIONS

UK Action on Hearing Loss’s
Translational Research Initiative for Hearing

Knowledge Hub: providing expert advice and guidance to industry and investors on hearing loss and tinnitus research and development, and market opportunities.
Partnership with Industry: helping industry to work with leading research groups and therapy area experts around the world.
Funding Scheme: supporting international translational research in hearing loss and tinnitus.
Patient Involvement: helping people with hearing loss and tinnitus get involved in research.
CLINICAL TRIAL STRATEGIES

- MRMC AD office: previous DOD-FDA Creative Solutions in Chem/Bio

- Expedited pathways
  - 2-Animal model rule
  - Breakthrough designations
  - Orphaned “technologies” rather than orphan disease?
  - Critical Path Innovation Meeting?
  - Office of Drug Development Tools Program?

- Guidance for research methodology
  - Standardization
  - New metrics beyond the “criterion standard” audiogram
GOALS

- Standardize/Guide Future Research
- Road Map Portfolios
- Continue open dialogue
- Enable Partnerships
E.3 Military Health Services Research Symposium (MHSRS), Ft. Lauderdale, FL, August, 2015

E.4 Association for Research in Otolaryngology (ARO) Mid-Winter Meeting, San Diego, CA, Feb 21, 2016

Disclaimer

The views expressed in this presentation are those of the author and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the U. S. Government.

INTRODUCTION

• Advancements in PIHL research have been slow to materialize

• Current issues facing scientists in this field include:
  – poor translation from animal to human model
  – study population access and other logistical concerns
  – targeted translational funding
  – undeveloped commercialization pathways
  – lack of unified study design guidance for investigations and investigators.
  – the heterogeneous state of PIHL research is not conducive to reliable comparisons of outcomes.
INTRODUCTION

• With the aim to remove such impediments to progress, the HCE’s PIHL Working Group offers a selection of laboratory, animal and clinical assessment protocol methodology guidelines developed through both evidence-based and collaborative expertise consensus.

• Target audiences: AGENTS OF CHANGE
  – Research investigators
  – Program sponsors
  – Professional societies
  – Publishers
  – Pharmaceutical developers

HEARING CENTER OF EXCELLENCE

• Public Law 110–417 Duncan Hunter National Defense Authorization Act (NDAA) for FY 2009, Section 721:
  – Secretary of Defense shall establish, within the DoD, centers of excellence (CoE) to include a CoE focused on the prevention, diagnosis, mitigation, treatment and rehabilitation of hearing loss and auditory system injury
  – to encourage and facilitate the conduct of research, development of best practices and clinical education
Military Noise

Military operations are inherently noisy

Ability to hear and communicate is critical for mission performance

Most hearing loss can be mitigated

Hearing loss can negatively impact operational effectiveness, medical readiness, and quality of life
**MILITARY NOISE = VA DISABILITY**

<table>
<thead>
<tr>
<th>Number of most prevalent service-connected disabilities of new compensation recipients</th>
<th>FY13</th>
<th>FY14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinnitus (#1)</td>
<td>135,229</td>
<td>140,288</td>
</tr>
<tr>
<td>Hearing Loss (#2)</td>
<td>80,186</td>
<td>80,171</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of most prevalent service-connected disabilities of all compensation recipients</th>
<th>FY13</th>
<th>FY14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinnitus (#1)</td>
<td>1,121,709</td>
<td>1,276,456</td>
</tr>
<tr>
<td>Hearing Loss (#2)</td>
<td>954,856</td>
<td>933,182</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of service-connected disabilities of all compensation recipients</th>
<th>FY13</th>
<th>FY14</th>
<th>% Change FY13 to FY14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory system</td>
<td>2,116,518</td>
<td>2,352,609</td>
<td>11%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benefit program</th>
<th>Number of recipients</th>
<th>Estimated average individual amount paid annually</th>
<th>Estimated total amount paid annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compensation</td>
<td>3,949,066</td>
<td>$13,712</td>
<td>$54.23 Billion</td>
</tr>
<tr>
<td>Service-Connected Death</td>
<td>383,263</td>
<td>$15,521</td>
<td>$5.94 Billion</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4,332,329</strong></td>
<td><strong>$13,863</strong></td>
<td><strong>$60.17 Billion</strong></td>
</tr>
</tbody>
</table>

~60% of Veterans claiming disability are claiming an auditory injury! Which doesn’t mean that ~60% of this is auditory injury thanks to complex VA algorithms, but still...
THE PIHL WORKING GROUP

The Pharmaceutical Interventions for Hearing Loss (PIHL) Working Group
• Chartered in 2012 by the HCE and supported with an administrative team
• Aligns inter-agency/institutional and interdisciplinary experts across this field
• Shared goals of supporting research and development of translational therapies for protection, rescue, and regeneration

Goals of the PIHL:
• Provide a platform for collaboration, discussion, networking and progress
• Review existing State of the Science
• Determine minimal acceptable level(s) of functional performance for any potential translational agents
• Develop and validate evidence-based laboratory, animal and clinical assessment protocol methodology guidelines
• Recommend appropriate standards and technologies

THE PIHL WORKING GROUP

• The Working Group is an open-invitation membership forum
  – Biennial State of the Science Symposia co-sponsored by the DOD HCE and ONR’s NIHL Program to provide a platform for discussion and dissemination of the advancements made.
  – Quarterly Teleconferences are held to disseminate accomplishments, discuss issues facing the working group and plan future lanes of effort.
  – Four Committees of the Working Group are:
    • Clinical Trials Committee
    • Animal Committee
    • Sound/Noise Committee
    • Ototoxicity Committee
PIHL GOALS

• Standardized requirements
  – Provide a target
  – Avoid misdirected efforts
  – Consider DoD safety/efficacy requirements

PIHL GOALS

• Organize and advocate for the field among funding agencies

• Facilitate conversations with Regulatory bodies to find solutions to bottlenecks
PIHL OUTCOMES

- **Meaningful coordination**
  - 2 State of the Science meetings
  - DOD and NIH Funding agencies
  - FDA
  - International communities of interest

- **Sound Repository** ([http://militarysounds.org/](http://militarysounds.org/)):
  - open-access online repository
  - researchers in the community can store, analyze and retrieve
  - sounds recorded in military environments
  - Recordings verified as having met specific requirements (calibration, specific reportable information about recording circumstances, etc.)
**PIHL OUTCOMES**

- **Knowledge Products**
  - Epidemiological picture of hearing loss in the DOD
  - PIHL Newsletters ([hearing.health.mil](http://hearing.health.mil))
    - Editions 1 and 2: Animal Guidance
  - **Edition 3: Clinical Guidance** - 9 documents
    - Edition 4: Sound Guidance – 6 documents
    - Edition 5: Animal Reviews – 2 documents
  - **Future Peer-Reviewed Journal Special Editions**
    - Otology & Neurotology: Clinical Guidance (currently in editorial stage)
    - Hearing Research: Noise Impacts in the Military & Mechanisms of Action (co-editors currently finalizing authors/articles)
    - TBD: Ototoxicity themed
  - **Future Systematic Review of PIHL Research Methodology**

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**WORKSHOP AGENDA**

1015 Introduction to Pharmaceutical Interventions for Hearing Loss (PIHL) and the Need for Standardizations in Research Design
Tanisha Hammill, MPH, MA; Mark Packer, MD

1030 Defining TTS and PTS in NIHL Intervention studies
Allen Ryan PhD, Sharon Kajawa PhD, Tanisha Hammill MPH, Colleen LePrell PhD, Jonathan Kil MD

1045 Guidelines for Auditory Threshold Measurement for Significant Threshold Shift (STS)
Kathleen Carapell, PhD, Michael Hoffer, MD, Tanisha Hamill, MPH, Jonathan Kil, MD, Colleen Le Prell, PhD

1100 Suprathreshold Manifestations of NIHL
Colleen Le Prell PhD, Douglas Erbhart PhD

1115 Measurements of Noise-Induced Tinnitus
James Henry, PhD (presented by Dawn Konrad-Martin PhD)

1130 Use of Otoacoustic Emissions to Assess the Efficacy of a Pharmaceutical Otoprotective Agent
Dawn Konrad-Martin PhD, Garret McMillan PhD, Lynne Marshall PhD, Judith Lapsley Miller PhD, Gayla Posing PhD

1145 Oxidative Damage and Inflammation Biomarkers: Strategies in Hearing Disorders
Gerald Haass, MD, Kedar Prasad, PhD

1200 Genetics of Noise-Induced Hearing Loss – A Link to Pharmaceutical Intervention
Royce Clifford, MD, MPH, Michael Hoffer, MD, Rick Rogers PhD
Good Clinical Practice Parameters for PIHL Studies

- At a Minimum: Should meet International Conference on Harmonization Guidelines (ICH) guidelines for clinical trials (Technical Requirements for Pharmaceuticals for Human Use)
- Should meet standards and guidelines of the American Speech Language Hearing Association (ASHA), American Academy of Audiology (AAA), American National Standards Institute (ANSI), as well as military standards and guidelines for test equipment, test environment, clinical procedures, and personnel where appropriate.

Sound Field Requirements and Equipment Standards

- Conducted inside a sound booth that meets specific standards.
  - ANSI S3.1 specifies maximum permissible ambient noise levels (MPANLs).
  - Maximum Permissible Ambient Noise Levels (MPANLs) differ based on test frequencies and transducer type (type of earphone, speaker for sound field testing, or bone conductor).
- ANSI S3.6 provides specifications and standards for audiometers
  - Annual calibration of audiometers at a minimum. More frequently if audiometer is moved.
  - Documented daily listening check or Bioacoustic Simulator
  - Tympanometric testing for middle ear function
Clinical Trials Personnel

- Principal Investigator (PI)
- Lead Study Coordinator
- Research Audiologist(s)
- Audiology Technician(s)
- Study Technician
- Biostatistician

TIP: Probably the most underestimated cost on a clinical trial is the personnel requirements and the need for constant availability of appropriate staff. Training, vacation and sick time, turnover, off hour and weekend availability must all be addressed.

Principal Investigator (PI):

- Overall responsibility for all elements of the clinical trial: study design, regulatory reviews and approvals, study implementation, recruitment, enrollment, study procedures (from consent to experimental elements) scientific analysis, and scholarly presentation, and reporting to institutional, regulatory or funding agencies. For auditory clinical trials the PI is generally an otolaryngologist or PhD audiologist.
Lead Study Coordinator:
Clinical Research Coordinator (CRC) or Project Director (PD)

- All administrative elements of the clinical trial: e.g., study submission documents including Investigators Brochure, Clinical Protocol, Case Report Forms (CRFs) monitoring study document submissions and Internal Review Board (IRB) approvals, implementing all monitoring systems, recruiting and tracking study participants, and coordinating across study sites for multicenter clinical trials.

TIP: Look for qualified personnel with a Masters of Public Health (MPH), a nursing degree, or relevant field with extra training in research and study coordination, design and monitoring, and certification from Society of Research Administrators International (SRA), Association of Clinical Research Professionals (ACRP) or the Society of Clinical Research Associates (SoCra).

Research Audiologist(s)

- The backbone of any clinical study for hearing and hearing loss
- Works with PI and study coordinator on study design and implementation
- Provides day to day oversight of all auditory assessments
- Audiologists responsible for all testing and recording of audiologic data
- In the US, licensed audiologist, with AuD or PhD depending on the role
Audiology Technicians

- In some cases, trained technicians may collect audiometric data
- Must be under supervision of audiologist and PI
- Must be dedicated to the study or have specifically dedicated time for the study

**TIP:** Certification required may vary by IRB, study type (single versus multi site), setting: military (DoD; HCP) or industrial. Council for Accreditation in Occupational Hearing Conservation (CAOHC), device specific training, and licensure laws. In some cases, a study technician may assist for study procedures other than audiology (equipment checks, scheduling, paperwork). Check your local requirements!

Study Statistician

- Critical Element of any team
- Initially involved in: Study Design, Statistical Methods for Data Analysis, Power Analysis, may work with data management throughout the study
- Later involved in: Presentation and Publication of Data
- Should have a background in statistics but also in acoustic science.
Procedures for Pure Tone Threshold Testing

- Detailed history including noise exposure and use of HPDs
- Otoscopy with referral to otolaryngologist if needed
- Tympanometry
- Conventional (.25-8 kHz) pure-tone air and bone conduction (0.5-4 kHz) audimetry at any frequency where air conduction is ≥ 15 dB. (Modified Hughson Westlake Procedure) Replicability check at 1 and 2 kHz

TIP: While not required, high frequency audiometry above 8 kHz can be considered if time and equipment allow. Its use for noise induced hearing loss has not been clearly confirmed.

Determination of TTS & PTS

- Noise “notch” typically occurs at 3, 4 or 6 kHz
- Temporary Threshold Shift (TTS) recovers within hours or days of noise exposure (typically 16-48 hours).
- Permanent Threshold Shift (PTS) is generally considered to be present if measured 3-4 weeks after the noise exposure. However, the availability of testing patients with no noise exposure during that time period and availability for testing afterwards must be considered in study design and duly noted in study design limitations.
- The subject should have no noise exposure at least 16 to 24 hours prior to each hearing test (with the exception of post-exposure TTS assessments).
**Significant Threshold Shift (STS)**

- Occupational Safety and Health (OSHA) definition of STS is an average threshold shift of ≥ 10 dB at 2, 3 and 4 kHz in the same ear.

- The Department of Defense (DoD) Defense Occupational and Environmental Health Readiness System-Hearing Conservation (DOEHSR-HC) guidelines use the same standard for determination of STS.

**TIP:** DOEHSR-HC also provides a guidance for early warning shift STS or early warning flag, which is defined as a 15 dB or greater change at 1, 2, 3, or 4 kHz in either ear.

---

**Determination of Pharmacologic Otoprotection**

- **First Do No Harm!** For every clinical trial, every effort must be made to prevent noise induced hearing loss including use of hearing protection devices (HPDs).

- The study design and criteria for determination of protection are dependent on the indication (protection from TTS versus STS) and the probable site of action (peripheral or central auditory system). The study must also be designed to capture short term (acute noise exposures) versus longer term (age related hearing loss) considerations.

**TIP:** While threshold data are the backbone of the study, additional measures may be needed depending on the drug and indication (e.g., word recognition, listening in noise, tinnitus measures, otoacoustic emissions). Be sure to rule out other pathologies with simple additions of otoscopy and tympanometry!
Study Design and Data Capture

- Prospective, double-blind, placebo-controlled Randomized Controlled Trial
- Reviewed and approved by an Institutional Review Board
- Subjects serve as their own control relative to baseline measures
- Challenges: Availability of test populations that unavoidably incur noise-induced hearing loss under HPDs in a relatively short period of time with standardized noise exposure

Study Elements in PIHL Investigation

- Study subjects and investigators are to be fully blinded to condition
- Experimental design – within-subjects serial testing
- Anticipated injury-imposing exposures from which to protect or treat
- Timely access to study populations
Summary

- Hearing loss a major fiscal issue for DoD, and a quality of life issue for affected soldiers/veterans
- Preserving situational awareness and preventing disability are urgent and compelling issues
- PIHL group actively discussing "best" approach for testing potential otoprotective therapeutics
- Information presented here represents guidance as shaped by discussion at PIHL meetings
DISCLOSURE

No financial conflicts of interest

The views expressed in this presentation are those of the author, a support contractor, and do not reflect the official policy or position of the Department of Defense, Department of Veterans Affairs, or the U. S. Government.

AGENDA

A Descriptive Analysis and Critique of Pharmaceutical Interventions for Hearing Loss (PIHL) Study Methods and Reporting in the Literature: A systematic review to inform research conduct, policy and culture

What is “PIHL”? Why review ALL of the literature? How? What does it tell us? So now we know...now what??
BACKGROUND


Studies like this one ^ kicked off this line of inquiry over 40 years ago!

Meanwhile...

DEPARTMENT OF VETERANS AFFAIRS DISABILITY AWARDS

...and investments have been made


BACKGROUND

Yet progress is stymied

- Silo’d efforts
- Lack of coordinated roadmap
- Lack of “gold standard” measures = lack of comparable outcomes
- Poor translation from animal models into human trials
- Lack of Repeatability
- No Accountability
Goals of the PIHL:
- Provide a platform for collaboration, discussion, networking and consensus → progress!
- Review existing State of the Science
- Recommend appropriate standards and technologies
- Develop and validate evidence-based laboratory, animal and clinical assessment protocol methodology guidelines
- DOD: Determine minimal acceptable level(s) of functional performance for any potential translational agents; manage DOD study populations; develop DOD acquisition pathway

A SYSTEMATIC REVIEW APPROACH

Protocol Development and PROSPERO Registration
http://www.crd.york.ac.uk/prospero/
registration #CRD42015027009
AIMS

- **Primary Aim 1**: To define, identify, characterize, and evaluate primary study method variables across PIHL literature including: study design, in vivo model selection, hearing injury exposures, hearing measures, drug pathway, drug mechanism or class, drug delivery, as well as study and investigator demographics.
- **Secondary Aim 1**: Using relevant standards and guidelines for reporting (CONSORT and ARRIVE), assess the quality of reported studies.
- **Secondary Aim 2**: To identify, evaluate and summarize any trends of correlation between methodologies utilized in study designs which could contribute to a "criterion standard" for future study design guidance
- **Primary Aim 2**: To translate findings into “best research practices” guidances and policy recommendations designed to inform and influence the FDA, Federal funding agencies and relevant journal editorial board audiences.

SEARCH STRATEGY

- Search parameters
  - Range of search/databases
  - Capturing PIHL studies is HARD because the first heterogeneous aspect of PIHL research is the way we talk about it!
  - Something to do with “Hearing”
  - Something to do with an “loss” of that hearing
  - Something to do with “chemical interventions” to those various processes
FIRST “BEST RESEARCH PRACTICE” IN PIHL

- Use whatever descriptors you want in your title, but for searchability, always INCLUDE THE KEYWORDS:
  - **“HEARING LOSS”**
    - Acoustic trauma, noise injury, SGN degeneration, cochlear damage, hair cell loss, etc. are all accurate, but there must be an umbrella term under which they can all fall, and I propose the clinically relevant, functional, end-game option – hearing loss.

- **“PHARMACEUTICAL”**
  - “Drug” doesn’t cover biologics, vitamins/nutriceuticals
  - Distinguishes from studies about surgical/device interventions

- **“NOISE” or “OTOTOXICITY”, as appropriate (sometimes both!)**

SEARCH STRATEGY

- **Inclusion**: search terms (almost 1,500 terms combined)
  - no date limit
  - no exclusion to the Boolean search (i.e., “NOT Ototoxic” cannot be used)

- **Exclusion criteria**:
  - performed in blinded title & abstract review
  - again in full text reviews

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>Primary target for intervention is not noise-induced hearing/tinnitus</td>
</tr>
<tr>
<td>Intervention is not a chemical agent</td>
</tr>
<tr>
<td>Other auditory conditions (congenital deafness, presbyscusis, sudden sensorineural, Meniere’s, etc.)</td>
</tr>
<tr>
<td>Regeneration study</td>
</tr>
<tr>
<td>Not original, cohort, prospective research (review, retrospective, case study, etc.)</td>
</tr>
<tr>
<td>Not an in vivo study</td>
</tr>
<tr>
<td>Not an intervention study (includes pathophysiology/etiology, delivery or diagnostic approaches, aim to cause HL without intervening to prevent/rescue HL)</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>
SEARCH RESULTS

- 3,492 articles retrieved
- +52 from alt sources; ~402 dups
- 3,142 articles to review
- 277 for full text review
- 58 excluded
- 219 studies reporting

- However! today is an interim analysis of 133 articles.
  - All 27 human from 219
  - 106 animal

SYSTEMATIC REVIEW
DATABASE CREATION & COLLECTION

LEVELS OF DATA COLLECTION
- Citation – “demographics”
- Study – species information/demographics
  - Human
  - Animal
- Exposure
  - Noise
    - Ototoxic – future study!
- Drugs
- Measures
- Intervention Arms (combine above as appropriately)
- Analysis (Primary Aims and Statistical Plan elements)
- Outcomes
  - Quality of reporting
PHARMACEUTICALS

- 200+ in these first 133 articles alone!
- Almost 100 mechanisms of action

Routes of Administration
- inhalation
- intraperitoneal
- intracocelear
- intragastric

- intramuscular
- intratympanic
- intravenous
- oral

- RWM application
- scala tympani
- subcutaneous

Mechanism:
- ampoule infusion
- centrifuge tubes
- chewable tablets
- dissolved in juice
- Dissolved in liquid
- effervescent tablets
- feed
- gavage
- gavage fed

- gelatin sponge
- Gelfoam
- hyaluronic acid gel
- infusion
- injection
- microcatheter
- microcatheter infusion pump
- micro-osmotic pump

- microsyringe
- mini-osmotic pump
- NA
- NR
- perfusion
- sit in chamber
- sende (probe)
- surgical
- tablet

NOISE SUMMARIES

Human Exposures:
- 3-14 Days Exposure
- 40-420 Impulse events (yet only 10 dB between these)
- 14-18 years of occupational means
  - 10 min - 5 hours daily exposures (no 8+ hour days?)
- 85-166 dB (when known)
- 12 unreported or unknown exposures (clinical presentation studies)

Animal Exposures:
- 3-700 (ave. 9.4) Impulse events, all between 135-176 dB SPL
- .025 - 60 Exposure Time (range)
- 4.2 Hr Exposure Time (average)
- 88-130 dB (111 dB average)
- 8 studies used multiple day exposures (1-14)
MEASURES

- (K = 27) PTA Measurement Frequencies

Not reported!

PTA Hearing Frequency (Hz)

MEASURES

- Human studies used an average of 5.1 measures per study
MEASURES

- ABR
- Animal naming test
- Biesinger grade
- Bone conduction
- Controlled Oral Word Association Test (COWA)
- Diary
- Drug test
- Endoscopy
- Hand blood flow
- Noise History
- Personal noise measurements/Dosimetry
- Psychoacoustical modulation transfer function (PMTF)
- Romberg/tandem Romberg Test
- Speech discrimination
- Structured Interview
- TEQAE
- THQ
- Tinnitus annoyance “today”
- Tinnitus Arnoynce (TAQ)
- Tinnitus Handicap Index (THI)
- Tinnitus loudness “right now”
- Tinnitus Loudness Questionnaire (TLQ)
- Tinnitus screener
- Tinnitus Severity Index (TSI)
- Tinnitus: Loudness Match
- Tinnitus: Patient global impression of change (PGIC)
- Tinnitus: visual analogue scale (VAS)
- Trail Making Test

11! All used in 1 or 2 studies.
Plus the MMI and mysterious TQ (K~5/ea)

ANALYSIS

Analytics:
- Subject sizes
- Aims [descriptive/summary]
- Statistical tests [descriptive/summary]

Future analyses:
- Qualitative Outcomes
- Quality of Reporting, in depth, quantitative
- Translation correlations from animal to human studies
NEXT STEPS

→ PIHL working group with these data to create and come to consensus on “Best Research Practices”

...and then what?

[Image of a man in a classic TV show scene]

KNOWLEDGE TRANSLATION

Step 1:

Step 2:
KINGDOMS TRANSLATION

Step 1:

CORRELATIONS AND TARGETED MESSAGING

- Are there author groups or regional targets for a particular change?
  - ENTs like surgical approaches to hearing measures and drug administration
  - Asian studies are less likely to report age of the animals used
- Are there journals which consistently accepting reports below standards for reporting animal studies (ARRIVE) or clinical trials (CONSORT) that we can reach out to, target for special issues?
- Are there interdisciplinary groups to target for consultation pools?
  - Statistics
  - I, Noise!
- Translation focus!
  - Talk about clinical relevance in humans when justifying animal model selection and discussing results. Very few articles did this overall.
  - Statistics and reporting for comparability
    - Availability of raw data
KNOWLEDGE TRANSLATION

Step 3: Follow the money...

NIH
NIDCD

Veterans Health Administration

Step 4: work with gatekeepers...

FDA

OSHA

NIOSH

Hearing Restoration Project

KNOWLEDGE TRANSLATION

TRANSLATIONAL SCIENCE STAKEHOLDER MANAGEMENT MODEL

Platform for community engagement, dialogue, consensus, by-in.

Communication of State-of-the-Science, best practices in PIHL research; Influence adoption of recommended best practices through approvals

SMEs; drivers of standards, first adopters of best practices.

Highly incentivized to utilize evidence-based research practices:
- to expedite regulatory processes
- increase chances for funding awards
- prestigious journal and/or conference dissemination of efforts
- all of which in turn strengthens the evidence base


Hammill TL. 2016. Presented in poster session at the 2017 Association for Research in Otolaryngology (ARO) Mid-Winter Meeting, Baltimore, MD.
SUMMARY

- PIHL research has languished for many years
- A lack of cohesive guidance for the field is partly to blame

- Why should you care?
  - PIHL research partners in research, on the front lines with these populations – public health and hearing conservationists
  - There needs to be a particular attention given to the collection of evidence for safety to the general population, particularly in light of the depth of supplements in this pipeline

- This review seeks to provide a pathway for PIHL researchers that can expedite through efficiency, creating opportunity to bring an equal level of evidence for both safety and benefit

QUESTIONS?

- THANK YOU!
- And thanks to the PIHL WG members, as well as Dr. Carlos Esquivel, Dr. Colleen Le Prell, Dr. Craig Champlin, Dr. Jose Betancourt, Dr. Karen Rascati, and Dr. James Wilson for their mentorship and guidance.

- Please visit the HCE website HEARING.HEALTH.MIL → Researchers → PIHL group for Newsletters and more information
- Tanisha.L.Hammill.ctr@mail.mil OR 619-933-6035
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>3AB</td>
<td>3-aminobenzamide</td>
</tr>
<tr>
<td>4-OHPBN</td>
<td>4-hydroxy phenyl N-tert-butyl nitroine</td>
</tr>
<tr>
<td>7NI</td>
<td>7-nitroindazole</td>
</tr>
<tr>
<td>AEBSF</td>
<td>4-[2-aminobenzal]benzenesulfonyl fluoride</td>
</tr>
<tr>
<td>AL</td>
<td>Action level</td>
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<tr>
<td>ALCAR</td>
<td>Acetyl-L-carnitine</td>
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<tr>
<td>aminoguanidine</td>
<td>aminoguanidine hemisulfate salt</td>
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<tr>
<td>APC</td>
<td>Activated protein C</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>ATRA</td>
<td>All-trans retinoic acid</td>
</tr>
<tr>
<td>ATSDR</td>
<td>Agency for Toxic Substances and Disease Registry</td>
</tr>
<tr>
<td>B12</td>
<td>cyanocobalamin</td>
</tr>
<tr>
<td>BDNF</td>
<td>Brain-derived neurotrophic factor</td>
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<tr>
<td>BRPs</td>
<td>Best Research Practices</td>
</tr>
<tr>
<td>BSO</td>
<td>L-buthionine-[S,R]-sulfoximine</td>
</tr>
<tr>
<td>C</td>
<td>Ceiling limit</td>
</tr>
<tr>
<td>Ca</td>
<td>Carcinogen</td>
</tr>
<tr>
<td>CAE</td>
<td>Carboxy alkyl esters</td>
</tr>
<tr>
<td>CAL</td>
<td>California</td>
</tr>
<tr>
<td>CDDO-Im</td>
<td>2-cyano-3,12 dioxooleana-1,9</td>
</tr>
<tr>
<td>Compound A</td>
<td>2-(4-acetoxyphenyl)-2-chloro-N-methyl-ethyl-ammonium chloride</td>
</tr>
<tr>
<td>CoQ10</td>
<td>Coenzyme Q10</td>
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<tr>
<td>COR</td>
<td>Curculigo orchiodes rhizoma extract</td>
</tr>
<tr>
<td>DFO</td>
<td>Deferoxamine mesylate</td>
</tr>
<tr>
<td>DHHS</td>
<td>Department of Health and Human Services</td>
</tr>
<tr>
<td>DHF</td>
<td>7,8-dihydroxyflavone</td>
</tr>
<tr>
<td>D-met</td>
<td>D-methionine</td>
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DNQX  6,7-dinitroquinoxaline-2,3-dione
DoD  Department of Defense
EdU  5-ethynyl-2′-deoxyuridine
EGF  epidermal growth factor
EL  Permissible exposure limit
EPO  erythropoietin
FA  Ferulic acid, 4-hydroxy 3-methoxycinnamic acid
FGF-1  Acidic fibroblast growth factor 1
GCK  ginsenoside compound K
GDNF  Glial cell line-derived neurotrophic factor
GEE  Glutathione monoethylester
GSHE  Glutathione monoethyl ester
HBO  Hyperbaric oxygenation
HES  Hydroxyethyl starch
HGF  Hepatocyte growth factor
HPN-07  2,4-disulfonyl a-phenyl tertiary butyl nitrone
HPN-07  disodium 2,4-disulfophenyl-N-tert-butylnitron
IBO  Isobaric oxygenation
IDLH  Immediately dangerous to life and health
JSI-124  Cucurbitacin I
L-NAC  L-n-acetylcysteine
L-NAME  L-N-Nitroarginine methyl ester
LPA  Lyosphosphatidic acid
MB  Methylene blue (3,7-bis(dimethylamino) phenazathionium chloride)
mCPP  Metachlorophenylpiperazine
Mg  Magnesium
mg/m3  Milligram per cubic meter
min  Minutes
NAC  N-Acetylcysteine
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>NDGA</td>
<td>Nordihydroguaiaretic acid</td>
</tr>
<tr>
<td>Nec-1</td>
<td>Necrostatin</td>
</tr>
<tr>
<td>NHP</td>
<td>Non-human primate</td>
</tr>
<tr>
<td>NIOSH</td>
<td>National Institute for Occupational Safety and Health</td>
</tr>
<tr>
<td>NNLA</td>
<td>N-nitro-L-arginine</td>
</tr>
<tr>
<td>NR</td>
<td>Nicotinamide riboside</td>
</tr>
<tr>
<td>NT-3</td>
<td>Neurotrophin-3</td>
</tr>
<tr>
<td>OSHA</td>
<td>Occupational Safety and Health Administration</td>
</tr>
<tr>
<td>OTC</td>
<td>2-oxothiazolidine-4-carboxy-late</td>
</tr>
<tr>
<td>PBN</td>
<td>Phenyl-N-tert-butyl nitrotrione</td>
</tr>
<tr>
<td>PDTC</td>
<td>Pyrroldine dithiocarbamate</td>
</tr>
<tr>
<td>PGE1</td>
<td>Alprostadil (prostaglandin E1)</td>
</tr>
<tr>
<td>PIHL</td>
<td>Pharmaceutical Interventions for Hearing Loss</td>
</tr>
<tr>
<td>PPADS</td>
<td>Pyridoxal-phosphate-6-azophenyl-2P,4P-disulphonic acid</td>
</tr>
<tr>
<td>PPEE</td>
<td>Purified polyphenolic extract of Ecklonia cava</td>
</tr>
<tr>
<td>PPM</td>
<td>Parts per million</td>
</tr>
<tr>
<td>PPT</td>
<td>Propyl(1H) pyrazole-1,3,5-triyl-trisphenol</td>
</tr>
<tr>
<td>PTS</td>
<td>Permanent threshold shift</td>
</tr>
<tr>
<td>QTer®</td>
<td>Coenzyme Q10 terclatrate</td>
</tr>
<tr>
<td>REL</td>
<td>Recommended exposure limit</td>
</tr>
<tr>
<td>R-PIA</td>
<td>R-N6-phenylisopropyladenosine</td>
</tr>
<tr>
<td>RU486</td>
<td>11-dimethyl-amino-phenyl derivative</td>
</tr>
<tr>
<td>SB</td>
<td>Scutellaria baicalensis extract</td>
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<tr>
<td>siAMPKa1</td>
<td>AMPKa1 siRNA</td>
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<tr>
<td>siRadixin</td>
<td>Radixin-siRNA</td>
</tr>
<tr>
<td>siROCK2</td>
<td>ROCK2-siRNA</td>
</tr>
<tr>
<td>SME</td>
<td>Subject matter expert</td>
</tr>
<tr>
<td>SNHL</td>
<td>Sensorineural Hearing Loss</td>
</tr>
<tr>
<td>SOD-PEG</td>
<td>Dismutase-polyethylene glycol</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<td>--------------</td>
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<tr>
<td>ST</td>
<td>Short-term exposure limit</td>
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<tr>
<td>T-817MA</td>
<td>1-{3-[2-(1-Benzothiophen-5-yl)ethoxy]propyl}azetidin-3-ol maleate</td>
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<tr>
<td>Tempol</td>
<td>4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl</td>
</tr>
<tr>
<td>TTS</td>
<td>Temporary threshold shift</td>
</tr>
<tr>
<td>TWA</td>
<td>Time weighted average</td>
</tr>
<tr>
<td>ug/m3</td>
<td>Microgram per cubic meter</td>
</tr>
<tr>
<td>VA</td>
<td>Veterans Affairs</td>
</tr>
<tr>
<td>VBA</td>
<td>Veterans Benefits Administration</td>
</tr>
</tbody>
</table>
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Vita

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With a Master of Arts degree in Religious Studies and Ethics from the Point Loma Nazarene University in San Diego, and a background as an Ethics instructor for the El Cajon Community College, Mrs. Hammill began her military support career with the Navy Medical Center San Diego, serving as the Human Subjects Protections Specialist and Research Assistant to the ENT Department. After completing a Master of Arts in Public Health with a focus in Administration from the San Diego State University in 2005, and with a rapidly growing clinical research program within the department, Mrs. Hammill took on the position of Clinical Research Administrator for NMCSD ENT. In 2011, after the HCE stood up in San Antonio, Texas, Mrs. Hammill transitioned to the DoD level. She began the PhD program in Translational Science at the University of Texas Health Science Center San Antonio in August 2014 and maintains professional certifications as a Clinical Research Administrator and Project Management Professional. She is married to a US Marine veteran with one young son at home.

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