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Hearing Loss, Lead (Pb) Exposure, and Noise: A Sound Approach to Ototoxicity Exploration

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Abstract

To determine the state of the research on ototoxic properties of Pb, evaluate possible synergistic effects with concurrent noise exposure, and identify opportunities to improve future research, we performed a review of the peer-reviewed literature to identify studies examining auditory damage due to Pb over the past fifty years. Thirty-eight studies (fourteen animals and twenty-four human) were reviewed. Of these, twenty-four suggested potential ototoxicity due to Pb exposure, while fourteen found no evidence of ototoxicity. More animal studies are needed, especially those investigating Pb exposure levels that are occupationally and environmentally relevant to humans. Further investigations into potential interactions of Pb in the auditory system with other hazards and compounds that elicit ototoxicity are also needed in animal models. To better assess the effects of Pb exposure on the human auditory system and the possibility of a synergism with noise, future epidemiological studies need to carefully consider and address four main areas of uncertainty: (1) hearing examination and quantification of hearing loss, (2) Pb exposure evaluation, (3) noise exposure evaluation, and (4) the personal characteristics of those exposed. Two potentially confounding factors, protective factors and mixtures of ototoxicants, also warrant further exploration.

Keywords

ototoxicity; hearing loss; lead (Pb); noise; exposure mixtures

Introduction

A wide variety of adverse social, psychological, occupational, and educational outcomes stem from one disease process: hearing loss (HL) (Seidman and Standring 2010). HL is the third most disabling global disease (World Health Organization 2008), with about 466 million sufferers globally (World Health Organization 2018). The increasingly high prevalence of adult-onset HL in developing nations (Stevens et al. 2013) is due at least in part to occupational noise exposures (Nelson et al. 2005). Moreover, while HL is

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often only thought of as a disease of the elderly, HL affects those of all ages, and is especially damaging to quality of life and academic and social performance in children, even when cases are mild (Wake et al. 2004, Tharpe et al. 2009). Once damaged, the sense of hearing cannot be fully restored. Even with our furthered understanding of ototoxicants and improvements in deciphering the mechanism behind noise-induced HL, workers continue to suffer from occupational HL at alarming rates (Masterson et al. 2016). This may be due to a combination of potentially ototoxic chemicals in the workplace alongside poor levels of compliance with programs to protect workers' hearing (Rabinowitz et al. 2018); many traditional challenges to occupational HL prevention continue to threaten workers' hearing health today (Kerr et al. 2017).

A number of types of substances have demonstrated ototoxic properties, including organic solvents, certain medications, asphyxiants, metals (Campo et al. 2013), and pesticides (Crawford et al. 2008). Of the various metals linked to ototoxicity, lead (Pb) has been most extensively examined, though evidence and mechanisms for Pb-induced damage still have not been fully elucidated. Pb ototoxicity is more heavily researched than other toxicant metals (e.g. Cd or Hg); however, the impacts of Pb on the auditory system have not been as extensively studied as are its well-known effects on the nervous (Mason et al. 2014) and cardiovascular systems (Solenkova et al. 2014), and, at high doses, on the hepatic and renal systems (Goswami et al. 2005). Pb is ubiquitous in many occupational and community settings due to its main current industrial purpose, use in Pb-acid storage batteries, and environmental contamination from past uses in gasoline, plumbing, and paint. Given these factors, a better understanding of combined exposures to ototoxic agents in settings where vulnerable populations may be exposed is essential for developing plans to prevent HL.

In the past, HL was traditionally associated with age or noise exposures. Today, modern research has demonstrated that chemicals such as styrene and aminoglycosides contribute to auditory damage as well (Morata et al. 2011, Schacht et al. 2012). Additionally, epidemiological studies have indicated that exposures to heavy metals, including arsenic, cadmium, Pb, manganese, and mercury, may be associated with an increased risk of HL (Anniko and Sarkady, Rybak 1992a).

Exposures to hazardous chemical mixtures represent an important area in risk assessment toxicology, as well as occupational health research (Simmons 1995). The US National Institute for Occupational Safety and Health (NIOSH) has highlighted the need for further research examining the relationship of metals to HL, especially those occurring in mixtures (Morata 2003). However, the impacts of Pb in combination with other hazards on the auditory system have not been extensively studied. Improvements in our understanding of the role of chemical agents causing HL are critical to preventing HL and identifying vulnerable workers in industries with multiple ototoxic exposures, as well as vulnerable communities and populations. As with Pb, noise is also ubiquitous in occupational and community settings (Lewis et al. 2013), and interactions between physical and chemical hazards in toxicology are underappreciated (Rider et al. 2014).

Reviews of Pb-induced ototoxicity are few and have not included a thorough examination of study methodology evaluating ototoxicity (Repko and Corum 1979, Otto and Fox 1993,

Araki et al. 2000, Johnson and Morata 2010a). A recent paper briefly reviewed a wide variety of divalent metals for ototoxic properties (Roth and Salvi 2016). However, that review focused on delineating potential mechanisms, and not on identifying opportunities to improving the design of future studies, as our review does. Another recent publication examining hearing impairment caused by occupational chemical exposures did assess ototoxicity of Pb, but did not evaluate study methodologies, as our review does (Johnson and Morata 2010b). In order to extensively review and thoroughly analyze both the methods and results of past studies on metal toxicity, this review focuses solely on Pb exposures to non-developmental life-stages, both alone and in combination with other agents. To capture all related studies, we have included studies on animals and humans. Animal studies can provide evidence of harm unconfounded by other variables, so we discuss these findings first. In contrast, epidemiological studies explore combinations of variables in uncontrolled, real-life settings, and offer insights that are more directly relevant to human exposures. Examining both types of literature are critical to determining the degree to which Pb contributes to HL in humans.

Methods

Firstly, the authors wish to make a point about modern search engines. While these are convenient and advantageous in many ways, they fall short in overcoming some of the deficiencies of the English language, namely heteronyms. While two search engines, Google Scholar and PubMed, were employed in our review, the use of tabulated search criteria resulted in a more accurate and efficient search of the literature. PubMed searches usually returned relevant papers, whereas Google Scholar searches were highly confounded by the heteronym lead, as in a horse to water. The heteronym hearing, as in a legal setting, also obfuscated the topic of interest. Over 122,000 hits were returned using keywords “lead” AND “hearing loss” on Google Scholar. For this reason, we relied heavily on PubMed’s tabulated search criteria which, when refined, returned under 200 hits.

Our PubMed search used both keywords and Medical Subject Heading (MeSH) terms relating to topics of metals, ototoxicity, and Pb in both animal and human studies. Articles found were evaluated for references to additional literature of interest. Review articles on general ototoxicants (some of which addressed combinations of noise and chemical exposure) were also consulted to compile references (Haider et al. 1990, Rybak 1992b, Cary et al. 1997, European Agency for Health and Safety at Work (Institution) 2009, Prasher 2009).

To determine that a paper appropriately addressed HL, six MeSH terms were used in a Boolean search with an OR operator. These are listed below. Establishing the paper’s relevance to Pb was more difficult. The NCBI MeSH term repository was essential for this aspect of the search due to the issues with heteronyms. The keyword “Pb” was also introduced to capture studies using the chemical abbreviation for “lead”.

The main NCBI Boolean search used is below for reproducibility of our findings:

(“Hearing”[Mesh]

OR “Hearing Loss, Mixed Conductive-Sensorineural”[Mesh]

OR “Hearing Loss”[Mesh]

OR “Persons With Hearing Impairments”[Mesh]

OR “Auditory Diseases, Central”[Mesh]

OR “Auditory Threshold”[Mesh])

AND

(“Lead” [Mesh] OR “Pb”)

Only literature published in English was considered in our search. Studies were excluded from this review if the outcome assessed was the vestibular system, conductive HL, or tinnitus; if auditory tests were used to measure cognition; if the goal of a study was reporting on the prevalence of hearing disorders; and if occupational or noise-induced HL were evaluated with no measure of Pb exposure. We next excluded all studies relating to developmental Pb exposures and auditory function including studies on animals *in utero* or in human children. While these studies may serve as additional evidence, the mechanisms and pathology are likely to be different, so we omitted these papers from our review. From the articles remaining, the references listed within the articles themselves, and literature found from previous reviews on ototoxicants, 36 papers were selected for inclusion in this review. These papers were grouped by the nature of research into studies performed with animals (n = 14) and human studies (n = 23).

From each selected study, key information was abstracted regarding the methodology used to perform and measure all predictor and outcome variables of interest, as well as study results. Each paper was analyzed for strengths and weaknesses, particularly with regards to the ototoxic mixtures and potential confounding factors. All studies were reviewed by a single author (KC).

Results

Animal experimental evidence

Thirteen studies in whole animals and one study in animal tissues were identified. Table 1 summarizes methods of animal study designs; the lengths of the studies, dosing regimens and animal types are shown for comparison. Study results, along with noteworthy outcomes, are shown in Table 2. Tables 1 and 2 are arranged in chronological order overall, and alphabetical order for studies occurring in the same year.

High Pb dose studies—Historic exploration into Pb ototoxicity involved high doses of Pb that caused frank toxicity. Of the thirteen *in vivo* studies, nine involved high doses of Pb. Eight of these caused animal death or weight loss due to Pb treatment, while one study used a high dose of Pb and euthanized animals two hours after treatment. Six of these eight studies established the strong possibility of alterations in the auditory system, and possible neural damage, following Pb exposure; however, these findings may have been confounded by systemic toxicity effects. Two studies noted no auditory effects (Wilpizeski and Vogel

1972, Fazakas et al. 2005), though these negative results could have resulted from very small sample size (i.e., Wilpizeski *et al.,* 1974), or the use of uncommon testing procedures (i.e., the auditory cortical evoked potentials and electrocorticography used by Fazakas et al., 2005).

Studies displaying positive results for auditory dysfunction following high doses of Pb predominately used auditory brainstem response (ABR) and analysis of thresholds or waveforms. ABR can be performed in humans and rodents; five main waves are measured as neuronal signals pass from the cochlea to the auditory cortex in the brain. Alterations in the amplitude or latency of these waves can be signals of pathology. Hearing thresholds, interpreted as waveforms present, but diminishing in amplitude as the stimulus presented quiets, are another measure of hearing ability. In humans, thresholds from 0–19 dB are considered within the normal hearing range. Thresholds of 20 dB or more demonstrate different degrees of HL; thresholds of 20–34 dB show mild HL, 35–49 dB show moderate HL, 50–64 moderately severe, 65–79 dB show severe, 80–94 dB show profound HL, and 95 dB and over show complete HL (Vos et al. 2015). The World Health Organization defines HL as thresholds at or above 25 dB in one or both ears for pure-tone single frequency audiometry (World Health Organization 2018). Mean auditory thresholds vary by species and stimuli (particularly the frequency or pitch), but are similar to humans (Zheng et al. 1999).

Takahashi *et al.* (1984) found a significant increase in latency of N1 and a significant increase in P1-N1 amplitude after the sixth day of treatment. A significantly longer latency of N1 action potential was observed by Yamamura *et al.* (1984). Output voltage lowered under 20 dB in the highest Pb treatment group of Yamamura *et al.* (1987). Whole nerve action potentials were elevated to 25 dB after five weeks of treatment in results from Yamamura *et al.* (1989). Histopathology explored by Gozdzik-Zolnierkiewicz *et al.* (1969) showed axonal degradation and demyelination in the vestibulocochlear nerve (VIII cranial nerve), but no pathology in inner ear cells or in the spiral ganglion.

The study that used a terminal procedure explored the effects of Pb, both Pb acetate (PbAc) and tetra ethyl Pb on cochlear microphonic and compound action potentials thresholds. In guinea pigs, auditory nerve compound action potentials were disrupted due to administration of Pb acetate and increased thresholds by 5–10 dB at high and mid frequencies (Tuncel et al. 2002). Threshold shifts in the tertra ethyl Pb group were significantly greater than controls.

Low Pb dose studies—The four studies that administered lower doses of Pb employed different measures of auditory function and generally demonstrated ototoxicity. Nagymajtényi *et al.* (1996) used electrocorticography, but in contrast to the study with negative results in a high dose of Pb, found a significant decrease in electrocorticography index in the auditory centers, and a significant increase in mean frequencies for the study's highest and longest treatment group. Liu et al. (2011) found changes in ABR wave I-V latencies in rats exposed to Pb acetate via gavage. Jamesdaniel *et al.* (2018) used ABR in mice to determine significant 8–12 dB shifts from baseline threshold at 4, 16, 24, and 32 kHz. In contrast, Carlson *et al.* (2018) did not find significant changes in threshold shifts or

distortion product otoacoustic emissions (DPOAEs) after Pb treatment, and no outer hair cell loss in the cochlea.

In vivo studies—The majority of animal studies included in this review are laboratory *in vivo* studies. However, one *in vitro* study of cochlear outer hair cells from adult guinea pigs is summarized in Table 1 and 2. This study showed alterations of neural signaling necessary for auditory processing following exposure to Pb. PbAc decreased outward potassium currents in adult pigmented guinea pigs outer hair cell explants (Liang et al. 2004).

Further *in vitro* studies on neurological tissues indicate possible mechanisms for Pb toxicity in the auditory system, though the following studies were not performed with auditory tissues. Nerve terminals from rat brains receiving Pb treatment impacted the crucial proton gradient of synaptic vesicles and decreased glutamate accumulation inside these synaptic vesicles (Borisova et al. 2011); this is related to auditory processing as glutamate is the primary neurotransmitter used in ascending auditory neurons (Raphael and Altschuler 2003).

Combinations of exposure—The included *in vivo* studies explored a variety of exposures involving Pb. Several studies showed ototoxic effects; for example, acute low Pb doses of PbAc caused delayed auditory wave latencies in rats, which were alleviated through doses of copper (Liu et al. 2011). Phenyl-tert-butyl-nitrone administration alleviated threshold shifts from tetra ethyl Pb to some degree (Tuncel et al. 2002). Other studies found negative results. Fazakas et al. (2005) suggested that alcohol administration counteracted the effects due to Pb, but changes in electrocorticography in the auditory center due to a combination of Pb, mercury, and alcohol administration were not significantly different from a control group (Fazakas et al. 2005).

In vivo studies are necessary to understand the combination of physical and chemical hazards that have been explored only in two recent studies. Carlson *et al.* (2018) did not observe any significant changes in thresholds from combinations of Pb and cadmium; Pb, cadmium and noise; or Pb and noise. Jamesdaniel *et al.* (2018) observed greater threshold shifts to animals exposed to both Pb and noise compared to mice exposed to Pb alone suggesting potentiation.

In conclusion, the majority of animal studies identified in this review point to a neurological source of damage and support the ototoxic properties of Pb.

Human studies

In reviewing the twenty-four included epidemiological studies (Table 3), we identified four areas of uncertainty and weakness in this literature: 1) hearing examination and HL quantification; 2) Pb exposure assessment; 3) noise exposure assessment; and 4) participant characteristics. We describe each of these in detail below.

Hearing examination and HL quantification—The largest area of concern and variation with epidemiologic study methodology was the varying quality and type of hearing examinations. Good hearing requires a functional outer, middle, and inner ear, and unimpeded transmission of neural signals from the vestibulocochlear nerve, through the

brainstem, to the primary auditory cortex in the cerebral cortex of the brain. An important need for both toxicological and epidemiological studies is to examine the location and mechanism of hearing damage due to Pb exposure, and its interaction with noise. For example, while noise-induced damage typically occurs as cochlear hair cell death, the toxicological studies suggest damage due to Pb take place in the neural processing networks. Without this knowledge, the optimal measure (or measures) of hearing is unclear.

The twenty-four included human studies used a range of hearing tests, including DPOAEs, pure-tone audiometry, and brainstem auditory evoked response (BAER), each of which measures different aspects of the hearing system. DPOAEs, used in two human studies, are best used to assess cochlear outer hair cell function. Audiometry, used in fifteen studies summarized for this review, identifies the lowest level of subjectively detectable sound. Finally BAER, also called brainstem auditory evoked potentials (BAEP), used in eleven studies, measures neuronal transmission of action potentials to the auditory center of the brain. As Pb is a known neurotoxicant, further exploration into modification of auditory neural processing through BAER is likely worth investigation in Pb ototoxicity studies. Past studies have found that correlations between pure-tone audiometry and DPOAEs may be poor (Engdahl et al. 2013). Determining the best auditory function measures for epidemiological analysis will require a more complete understanding of mechanisms surrounding Pb ototoxicity.

Regardless of the test used, a quiet environment is necessary to ensure accurate hearing measurements. Four studies described the environment where tests occurred; background noise levels during these tests ranged from a “quiet area” (Counter and Buchanan 2002) to a sound-treated chamber (Park et al. 2010). The background levels of 30 (Hwang et al. 2009) and 50 dB (Wu et al. 2000) in two human studies are troubling, as normal thresholds are in the range of 0–20 dB. Prior to testing, tympanometry and visual inspection of the tympanic membrane to rule out ear infections or obstructions are needed. However, these tests were only described by one (Farahat et al. 1997) of the twenty-four studies.

Temporary threshold shifts due to noise exposure are another important consideration that could substantially alter the results of hearing tests and attenuate potential relationships between Pb, noise, and HL. Only two of the twenty-four human studies gave details on the timing of tests after the last exposure to high noise: fourteen (Wu et al. 2000) and sixteen (Chuang et al. 2007) hours of quiet, respectively.

Finally, due to the resilient nature of the hearing system (Pepler et al. 2014), it may be essential to rely on multiple tests to determine deficits in hearing function. To address this limitation, we recommend use of BAER to evaluate auditory neural processing, in combination with pure-tone audiometry to evaluate perception of sound.

Pb exposure analysis—Pb levels, measured in twenty-two of the twenty-four studies, were the most frequently used assessment technique. Other techniques included measurements of airborne concentrations of Pb (used in one study) and measurement of blood Pb in fingernails (used in one study). While blood lead levels (BLLs) may be representative of recent exposures, they do not account for the accumulation of Pb in the

bones following chronic exposure. Blood Pb has a half-life of about 30 days (Roberts et al. 2001), depending on initial levels, but also represents an equilibrium of the body burden carried in the bone. Bone Pb has a half-life over decades or longer (Wilker et al. 2011) . Two epidemiological studies used time-weighted averaging approaches to address the critical issues of exposure timing and intensity (Hirata and Kosaka 1993, Bleecker et al. 2003). One study measured the duration of exposure and Pb concentrations in ambient air (Hirata and Kosaka 1993), and both studies investigated the gold standard: individual monitoring of past BLLs from workers' five-year history. Park et al. (2010) took advantage of a recent development in measuring cumulative Pb exposure and used X-ray fluorescence to quantify Pb in bone. Use of this approach should increase the ability to accurately estimate metals exposure over long periods of time where BLLs are not especially meaningful.

Noise exposure assessment—Noise exposure is a major concern in occupational studies, since noise is a nearly ubiquitous occupational exposure. In some workplaces, Pb and noise exposure may co-occur, requiring an even more thoughtful exposure assessment to evaluate the exposures concurrently. Five (Farahat et al. 1997, Wu et al. 2000, Bleecker et al. 2003, Chuang et al. 2007, Hwang et al. 2009) of the twenty included occupational studies suggested HL in workers exposed to both noise and metals greater than expected for the amount of noise exposure alone. However, none of these studies provided sufficient information on the levels of occupational noise to which workers were exposed. Only one study investigated a link between noise exposure and heavy metals exposures for mining occupations (Saunders et al. 2013). The findings were inconclusive due to confounding issues of poor health as well as the large number of statistical analyses performed on multiple metals.

Quantification of environmental or leisure noise exposure is also critical. Of the twenty-four epidemiological studies included, two (Choi et al. 2012, Huh et al. 2016) included some adjustments and exploration into sources of noise that were non-occupational. Firearms create unique blast noise exposure, which is a threat to the entirety of the hearing system. There is also potential of additional Pb exposure from the use of firearms. Moreover, the use of guns is often correlated with high occupational noise exposure (Agrawal et al. 2010). Determination of leisure activities and community settings where loud noise exposures occur is essential. Communities feature multiple sources of noise exposure – e.g., transportation (Neitzel et al. 2012) – and all of these sources must be assessed to comprehensively evaluate the risk of HL with or without the presence of Pb.

Participant characteristics—Demographic information for participants was difficult to evaluate in a number of human studies. Every study listed participant age ranges and accounted for increased HL with age; however, this was often confounded by Pb exposure metrics that also increased with age or duration of employment. Given the correlation between these factors, more thoughtful analysis is needed. As HL levels have been found to vary by race (Sun et al. 2014, Hoffman et al. 2017) and income level (Chou et al. 2015), detailed information on participants characteristics is necessary for a clear understanding of possible confounders. Choi et al. (2012) had a great deal of information on their participants and detailed hearing outcomes as significantly different for non-Hisapnic whites and non-

Hispanic blacks; this study also found borderline significant differences between BLL and threshold levels for Mexican-Americans and non-Hispanic whites.

Potential confounders—In addition to these four sources of uncertainty in the identified studies described above, there are two major areas of potential confounding (protective factors and exposures to mixtures of ototoxicants) that need to be addressed more systematically. These are described below.

Protective Factors.: Factors which could improve the health of the hearing system and/or lower levels of Pb in the system must also be accounted for in human studies. High dietary intakes of iron and zinc have been shown to decrease the absorption of Pb (Goyer 1997). This may modify the effects of exposure to Pb in the ambient environment. Chuang et al. (2007) examined possible protective levels of selenium and found them significant. Araki et al. (1992) and Hwang et al. (2009) both accounted for levels of zinc and copper in the blood, which are essential metals and can limit uptake of more non-essential metal uptake by the body. To account for these dietary factors, a dietary survey must be used, as levels of zinc and iron in the blood are generally held in strict homeostatic levels not reflective of intake. Hearing protection offers workers and other exposed individuals protection against high noise, and can dramatically modify ambient exposure levels. None of the studies in this review accounted for hearing protection, even though this can attenuate exposures over 30 dB (Sayler et al. 2018). Therefore, assessment of exposure attenuation provided by hearing protectors must be included in epidemiological studies.

Exposure to mixtures of ototoxicants.: The number of known ototoxicants has increased in recent years; a partial list of the most relevant exposures that should be considered includes: smoke, drugs, solvents, and other potential metals. Adequate control of these measures in epidemiological studies requires large data sets and extensive participant information. Choi et al. (2012) used a large data set and included measures of Pb, cadmium, occupationally-related noise exposures, and non-occupational noise exposures. Smoking and environmental tobacco smoke are important exposures, although self-reported exposures have been shown to be unreliable (George et al. 2006). Both active and passive exposures to smoke should be assessed, as literature has shown a link between second hand smoke and HL in adolescents (Lalwani 2011). One study we summarized had detailed questionnaire data on participant smoking and was able to use pack-years in linear regression models (Park et al. 2010).

Powerful pharmaceutical agents, including cisplatin and aminoglycoside antibiotics, can cause damage to the auditory system (Schacht et al. 2012). Other drugs, including the commonly used pain medications aspirin and ibuprofen, as well as the angiotensin converting enzyme (ACE) inhibitor Ramipril, can cause tinnitus, temporary HL, or permanent HL (Bisht and Bist 2011). One of the studies from our review documented participant ototoxic drugs by self-report (Choi et al. 2012) and one study discussed likely exposures to ototoxic medications for their participants (Saunders et al. 2013).

Solvents, including toluene, styrene, xylene, carbon disulfide, and trichloroethylene, exhibit ototoxic properties (Hughes and Hunting 2013). Styrene, for example, exacerbates HL in the presence of concurrent noise exposures (Mäkitie et al. 2003), and jet fuel (a mixture of

chemicals) can cause HL and has potentiate HL from noise (Fechter et al. 2007, Guthrie et al. 2014). None of these twenty-four human studies assessed possible solvent exposure.

While properties of lead ototoxicity are unclear at this time, ototoxic properties of other metals have been reported and are less researched. The degree that metals other than Pb - e.g., mercury, cadmium, and arsenic – may influence hearing outcomes observed in epidemiological studies. Dietary reports and occupational histories, which were not assessed by any of these studies, are needed to account for comprehensive exposure assessment of essential and non-essential metal exposures. Biological markers were used for all twenty-four of the human studies.

Future opportunities—Accurately examining potential modification and confounding of Pb ototoxicity by noise exposures will allow for more protective health policies and procedures. Workers exposed to Pb have been shown to have higher levels of oxidative stress (Khan et al. 2008). These levels may have negative effects on their hearing ability. Encouragingly, changes to neurobehavioral performance have been shown to be reversible in Pb workers when exposures were reduced (Chuang et al. 2005). This may also be the case for negative effects of Pb on hearing.

Relevant health policy changes have recently occurred for environmental Pb exposures. In 2012, the CDC lowered the community action limit of Pb in the blood to 5 μg/dL (CDC 2012). Conversely, the Occupational Safety and Health Administration has not updated its BLL standards since 1978 (National Toxicology Program 2003). This agency requires workers whose BLL are at or above a 40 μg/dL limit to receive medical examinations. The medical provisions of 29 CFR § 1910.1025 could be amended to require a hearing examination to assess possible influence of Pb on auditory outcomes. This modification could assist in investigating the links of Pb and HL.

Publication of all studies exploring the ototoxic nature of Pb is needed, whether outcomes are positive or negative. While the results of the available literature suggest some consensus of ototoxic findings, it is worth considering that these results may have been influenced by publication bias and the relative absence of published studies with negative results (Song et al. 2014).

Conclusions

As our understanding of the impacts of ototoxic exposures on the auditory system expands, and we better understand complex interactions in dynamic biological systems, it is important to evaluate the role that both chemical and physical agents play in the hearing system and how they interact together. Overall, the thirty-eight studies included in this review did not show a clear relationship between Pb exposure and auditory health outcomes. At environmentally and occupationally relevant doses, the epidemiological evidence from twenty-four human studies seems to provide stronger support at this time than data from the fourteen animal studies, many of which focused on much higher exposures. Collectively, the studies suggest a possible relationship between Pb and HL and hint at an interaction with noise-related HL pathology. Future studies should address the four areas

of uncertainty identified here: hearing examination and HL quantification; Pb exposure assessment; noise exposure assessment; and participant characteristics. Additionally, studies must better address potential confounding from protective factors and exposures to mixtures of ototoxicants. Further studies are essential to developing a better comprehension of the Pb exposure levels of concern and the physiological processes that are most vulnerable to exposure.

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Table 1.

Features of thirteen *in vivo* with one *in vitro* Pb ototxicity toxicology studies

Study (by first author)	Animal	N	Age	Type of Pb	Dose	Study length	Exposure Assessment
A) *IN VIVO* STUDIES							
Gozdzik-Zolnierkie wicz, T. (1969)	Guinea Pig	10 C; 40 Pb	300–350 g	1 % $Pb/No_{3/2}$	ip injections 300 mg/kg once a day	7 weeks	310–420 μg/dL Estimated: 0.025–0.33 mg % control and 0.31–0.42 mg % Pb exposed
Wilpizeski, C. (1974)	Squirrel Monkey	12 Pb	Adult	Pb oxide (red Pb powder)	[preliminary treatments of peritoneal cavity 1 gram Pb foil (N = 5); nasal spray of PbAc & red Pb] peroral injection 0.5 mL once a day	5 to 24 weeks; varied for individual monkey	BLL:Control 53 ± 51 μg/% Pb 338 ± 225 μg/%
Takahashi, Y. (1984)	Sprague-Dawley rats (male)	4 C; 6 Pb	11 weeks/230–320 g	0.1 mM PbAc	ip injection 1 mL/100 g	Injected for four days. Measurements on days 1, 2, 3, 6, 9, and 11	Control > 10 μg/dL 267 ± 19 μg/dL
Yamamura, K. (1984).	Guinea Pig – Hartley albino	10 C, 13 in 10 mg, 10 in 15 mg, 20 in 20 mg	9 weeks/320 g	1 % PbAc	ip injection once a week of 0, 10, 15 or 20 mg	5 weeks	30 ± 14 μg/dL 154 ± 40 μg/dL 153 ± 46 μg/dL
Yamamura K. (1987)	Albino Hartley guinea pigs	10 C, 10 in 10 mg, 20 in 15 mg, 20 in 20 mg	9 weeks	1 % water solution PbAc	ip injection once a week of 0, 10, 15 or 20 mg	5 weeks	4.9 ± 2.9 μg/dL 123 ± 39 μg/dL 102 ± 30 μg/dL 134 ± 52 μg/dL
Yamamura K. (1989)	Albino Hartley guinea pigs (male)	20 C; 19 in 2 wks; in 4 wks; 20 in 5 wks	5 weeks of age or less	1 % water solution PbAc	ip injection once a week; control; 20 mg/ week	Control; 2 weeks; 4 weeks; 5 weeks	4.5 ± 2.4 μg/dL 80 ± 40 μg/dL 126 ± 19 μg/dL 124 ± 53 μg/dL
Hotta S. (1996)	Albino Hartley guinea pigs (male)	24 C; 8 in 2 wk; 8 in 4 wk; 21 in 4 wk + noise	Over 5 weeks of age	1 % solution PbAc	ip injection; 20 mg/week	Control; 2 weeks; 4 weeks (± noise);	3.2 + 1.5 μg/dL 139 + 29 μg/dL 165 + 42 μg/dL
Nagymajtényi, L. (1996)	Wistar rats (male)	8 per group, 12 treatment variations of Pb dose and treatment time	10 weeks old	PbAc dissolved in distilled water; 0.1 mL/ 100g body weight	Gavage 80, 160, and 320 mg/kg body weight for 5 days a week	4 weeks; 8 weeks; 12 weeks	None given
Tuncel, U. (2002).	2/NCR Guinea Pigs	5 per group oil C; ethanol C; PbAc-ethanol; TEPb-oil	–	PbAc and TEPb	ip injections PbAc 50 mg/kg; TEPb 42.7 mg/kg	Recordings followed 120 minutes after injection	tetraethyl Pb: 45.2–47.2 μg/dL PbAc: 45.2–47.2 μg/dL
Fazakas, Z. (2005).	Wistar rats	10 per group low-Pb; high-Pb; low-Pb+Al; high-	12 weeks	PbAc dissolved in distilled water (with 5 %	Gavage five days a week 80 mg/kg and 320 mg/kg	12 weeks	–

Study (by first author)	Animal	N	Age	Type of Pb	Dose	Study length	Exposure Assessment
		Pb+Al; Pb-low+Hg; Pb-low+Hg+Al		v/v ethanol or 0.4 mg/kg mercuric chloride)			
Liu, S. (2011).	Wistar rats	C: 5 M/5F Pb: 5M/5F Pb+Cu 5M/5F	140 – 270 g	PbAc	Gavage of 4.0 mg/kg	30 days	Pb: M 1.2 ± 0.09 µg/dL, F 0.8 ± 0.02 µg/dL
Carlson, K. (2018)	CBA/Ca J mice	C: 16 M 0.03–Pb: 8 M 1-Pb: 8 M 3–Pb: 16 M Pb+Cd: 9 M Pb+Noise: 14 M Pb+Cd+Noise: 7 M	5 weeks	PbAc from 2 % w/v solution	In drinking water 0.03, 1, and 3 mM dissolved in Milli-Q water	Final ABR after 10 weeks and tissues collected after 11 weeks Pb	BLL (µg/dL): 0.03 mM Pb – 3 ± 0.4 1 mM Pb – 39 ± 5 3 mM Pb – 60 ± 7 3 mM Pb+Cd –58 ± 2 3 mM Pb+Noise – 57 ± 4 3 mM Pb+Cd+Noise – 59 ± 4 Bone (mg/kg): Fem. 3 mM Pb – 287 ± 45 Tib. 3 mM Pb – 216 ± 51 Fem. 3 mM Pb+Cd – 236 ± 24 Tib. 3 mM Pb+Cd – 206 ± 23
Jamesdaniel, S. (2018)	C57BL/6 mice	C: 6 Pb: 6 Pb+Noise: 6	4 weeks + 5 days acclimatized	PbAc	In drinking water 2 mM PbAc	28 days	BLL (µg/dL): Pb – 293 ± 67 Pb+Noise – 319 ± 44
B) *IN VITRO* STUDY							
Liang, G.-H. (2004).	Guinea pig cochlear cells	3–4 outer hair cells per concentration	Adult	PbAc	0.1, 1.0, 10, 100 µM baths	–	–

* blood Pb levels were not reported for treatment of 10 mg Pb

PbAc = lead acetate; TEPb = tetraethyl lead; C = control; M = male; F = female; ip = intraperitoneal

Table 2.

Outcomes and conclusions summarized for fourteen toxicology Pb ototoxicity studies

Study	Outcomes and conclusions	Other
In Vivo Studies		
Gozdzik-Zolnierkiewicz, T. (1969)	• Temporal bone analysis was done with silver impregnation for 16 animals: Sensory cells in inner ear, spiral, and vestibular ganglion displayed no pathology. • Examine VIII nerve pathology was normal in five animals and lesions including demyelination and axonal degeneration were present in eleven. • Sudan black staining was carried out in 16 animals: four were normal; segmental demyelination and axonal degeneration observed in twelve.	• Eight animals died. • All remaining had systemic toxicity (weight loss and weakness) due to Pb. • Five surviving animals showed paralysis of limbs.
Wilpizeski, C. (1974)	• Pure tone detection thresholds trained shock avoidance showed hearing within normal ranges throughout the experiment (N = 2, treated for 10 and 21 weeks). • Temporal bone analyses and VIII nerve fiber study showed no damage to hair cells or demylenation (N = 3).	• Five died during treatment and two were sacrificed when near death. • Two developed arm and leg transitory paresis. • Severe weight loss was observed, however vomiting diarrhea and anorexia were not.
Takahashi, Y. (1984)	• Latency of N1 was significantly increased after day 2. • P2 latency was significantly increased over the control after day 3. • The amplitude between P1 and N1 increased on day 1, but was not significantly different on day 2 or 3. • After day 6, P1-N1 amplitude was again significantly different.	• Body weight decreased substantially due to Pb treatment initially. • At day 8, treatment weights were no longer significantly different from controls. • Hematocrit significantly decreased due to Pb treatment at day 6.
Yamamura, K. (1984)	• No changes to pseudo threshold or maximum output voltages were observed between control and all three experimental groups. • Action potential latency of N1 was significantly longer in the highest exposure group than the control. • Highest exposure conditions required a greater sound intensity (dB) to illicit similar action potential maximum output voltage regressions in comparison to control.	• All experimental animals lost weight on average. • Three died in 10 mg group • Four died in 15 mg group • Fourteen died in 20 mg group
Yamamura K. (1987)	• No changes in cochlear microphonics, either the maximum output voltage or the pseudothreshold. • Input-output function of action potential was different in highest exposure – output voltage was reduced especially below 20 dB (indicating VIII nerve axonal impairment).	• One died in 10 mg group • Five died in 15 mg group • Eight died in 20 mg group
Yamamura K. (1989)	• High-dose Pb exposure caused dysfunction of the VIII nerve. • Whole nerve action potentials elevated across treatment lengths; control was lowest, with all treatments compared to control 2 wks was 10 dB higher, 4 wks was 20 dB higher, and 5 wks was 25 dB higher.	• Three died in 2 wk group • Twelve died in 4 wk group • Twelve died in 5 wk group
Hotta S. (1996)	• Pb treatment alone did not cause cochlear electrophysiological changes. • Potassium ion concentration in the scala media was not altered. • Pb + noise groups displayed a significant decrease in AP output voltage from both control and Pb groups. • Pb + noise CM output and intensity were significantly lowered due to Pb and noise. • Pb + noise EP latency was significantly longer than controls and the combined exposure groups showed a lowered mean absolute value of negative potential.	• 6 died in 4-week group not exposed to noise. • 14 died in 4-week group exposed to noise. • No animals showed hind limb paralysis.
Nagymajtényi, L. (1996)	• Electrocorticogram from auditory centers showed decreases in amplitudes that were not significant, however displayed trends with dose and time. • Increases in mean frequencies also trended with dose and time, but were only significantly different from control in the 320 mg/kg for 12 weeks group. • Decreases in auditory electrocorticography – index again trended with dose and treatment time and were significantly different from controls only at the 320 mg/kg for 12 weeks group.	• Relative weights of organs from treated rats did not differ significantly from controls.
Tuncel, U. (2002).	• Acute hearing loss within two hours of exposure. • TEPb had a higher degree of toxicity to cochlea, though Pb content is equal to the PbAc solution. • Compound action potential thresholds were elevated in the Pb acetate group over controls 5–10 dB and significant from tested frequencies 4–40 kHz TEPb exposure significant at 20 and 24 kHz.	• Animals were euthanized 120 minutes after baseline recordings. • No changes in cochlear microphonics or compound action potential at single injection doses of 20 mg/kg Pb acetate and 17.1 mg/kg TEPb.

Study	Outcomes and conclusions	Other
	• Cochlear microphonics isopotential curves were not significantly different.	• Results at doses in the study were not seen after 60 minutes of treatment.
Fazakas, Z. (2005).	• Analysis of total electrocorticography in the auditory centers showed decreases in delta activity for the high Pb dose and Pb+Hg+Alcohol group. These changes were not shown as significant. • Changes in auditory cortical evoked potential latency and durations following acoustic stimulation of 1 Hz 40 dB was not pronounced (and not shown).	• Weight gain in the high Pb group was significantly lowered. • Liver/brain weight was significantly lower in the Pb-high group, Pb-high+Hg, and Pb+Hg+alcohol. Lung/brain weight was also significantly lower in the Pb-high group.
Liu, S. (2011).	• Significantly increased latencies for all ABR waves I-V were observed after Pb treatment, especially in males. • Amplitudes, especially for waves I and II were reduced, and to a greater degree in males.	• No animal loss or measures of systemic toxicity were reported. • Latencies of waves I-V in the Pb+Cu group were significantly lower than the Pb group.
Carlson, K. (2018)	• No cochlear outer hair cell loss was observed due to Pb. • Pb exposure did not cause significant changes in ABR or DPOAEs • No significant changes in ABR peak and latency were observed due to Pb treatment. • Potentiation due to Pb and noise exposures were not observed in ABR results or outer hair cell counts. • Pb and Cd together did not alter auditory results observed from the highest Pb treatment alone.	• One animal died due to unrelated causes (urologic syndrome). • Mild lesions in the kidney were observed in 91% of 3 mM Pb: karyomegaly in the S3 tubular epithelium.
Jamesdaniel, S. (2018)	• Pb treatment induced shifts of 8–12 dB (this was significant at the click, 4, 16, 24, and 32 kHz). • Pb treatment significantly downregulated oxidative stress genes Sod1, Prdx4, and Idh1 in cochlear RNA • Pb and noise treated animals had threshold shifts of 10–25 dB significantly higher than shifts due to noise exposure alone at the click stimulus, 4 and 32 kHz.	• Normal weight gain was not altered.
In vitro Study		
Liang, G.-H. (2004).	• Potassium current was reduced over time; this reduction was dose dependent. • Outward voltage-gated potassium relative current increased with increasing doses of Pb. • After washing Pb, these changes were not reversed. • Changes are small and are not indicative of causing hearing loss.	• Cells selected were middle to apical areas of the cochlea; cells sensitive to mid- and low-frequency sounds.

Table 3.

Methodological features of twenty-four epidemiological Pb ototoxicity studies

#	Type	First Author (Year)	N	Sex (F/M)	Mean Age	Pb Exposure Setting	Place	Hearing Test	Pb Measure	Noise	Metals
1	Cross-sectional	Baloh, R. (1979)	69 (64 aud.); 35 (31 aud.) controls		43 (Spivey et al. 1979) (sd=11)	Secondary Pb smelter – refining, and recasting Pb from auto batteries; controls from aluminum processing facility(Spivey et al. 1979)	US – southern CA	Pure-tone conduction; impedance studies; speech recog.	Current BLL 61 (13) μg/100mL; Longitudinal BLL 60 (14) μg/100mL	No	As
2	Prospective	Spivey, G. (1980)	69 (64 aud.); 35 (31 aud.) controls	-	-	Secondary Pb smelter; controls from aluminum processing facility	US – southern CA	Pure tone conduction; impedance studies; speech recog.	Follow-up BLL 66 (13) μg/dL;	No	No
3	Cross-sectional	Holdstein, Y. (1986)	57; Older: 16 exposed and 20 controls	Older exposed 10 F/6 M	Young (8-17); Older (18-56)	Ingestion of Pb-contaminated food source for 1-2 years, study was conducted one year later		Pure-tone thresholds and BAER	Prior BLL were averaged with new levels. Means of older: 31.2 μg/dL, prior 43.4 μg/dL	No	No
4	Cross-sectional	Lille, F. (1988)	13 Pb workers; 20 controls	3 F/10 M	37 (sd=10)	Occupationally exposed to inorganic Pb compounds	-	BAEP	Mean BLL 100 μg/dL (range 27-240)	No	No
5	Cross-sectional	Araki, S. (1992)	22 workers; 14 controls	22 M	Median48 (range 32-58)	Gun metal foundry workers	-	Auditory event-related potential	Median BLL 30 μg/dL (range 12-59) (UPb values not reported)	No	Zn, Cu
6	Cross-sectional	Discalzi, G.L. (1992)	49 workers; 49 controls (ASM)	12 F/ 37 M	34 (sd=11)	31 from Pb battery factories; 7 from the ceramic industry; 4 Pb contaminated wine; 7 misc. occupational exposures	Europe	BAEP	Mean BLL 55 (16) μg/dL; mean 3-year BLL average 54 (16) μg/dL	No	No
7	Cross-sectional	Discalzi, G. (1993)	22 workers; 22 controls	5 F/17 M	35 (sd=12)	Pb storage battery factory workers	Italy	BAER	BLL 48 (sd = 11) μg/dL	No	No
8	Cross-sectional	Hirata, M. (1993)	41 Pb workers/39 controls	All M	19 to 58	Pb-exposed workers from 4 factories and controls from nylon factory.	Japan	ABR	Current BLL and TWA from the past 5 years.	No	No
9	Cross-sectional	Murata, K. (1993)	22 workers; 22 controls	22 M	Range 32-59	Gun metal foundry worker	-	BAEP	Mean BLL 39 μg/dL (range 16-64 μg/dL)	No	No

#	Type	First Author (Year)	N	Sex (F/M)	Mean Age	Pb Exposure Setting	Place	Hearing Test	Pb Measure	Noise	Metals
10	Cross-sectional	Murata, K. (1995)	36 Pb workers/15 textile controls	All F	21 to 35	Glass workers (7.8 average years in factory)	China	BAEP	Mean BLL 56 μg/dL (range 26-79); Air concentrations 0.4-1.2 mg/m^3	No	No
11	Cross-sectional	Farahat T. M. (1997)	45 workers/45 controls	--	20 to 40	Printing facility and controls from textile factory	Egypt	Pure-tone thresholds	BLL (worker mean 37 μg/dL; control mean 12 μg/dL)	40-50 dB	No
12	Cross-sectional	Forst, L. S. (1997)	183 workers	12 F/ 171 M	19 to 65	Private business. 70% white, 22% African American, 8% Hispanic	US	Pure-tone thresholds	BLL 1-8 μg/dL (5 μg/dL 50th percentile)	No	No
13	Cross-sectional	Fujimura, Y. (1998)	2 workers/42 controls	2 M	50 & 57	Pb smelting	-	BAEP	Mean BLL 104 & 79 μg/dL (followed for 12 and 15 months)	No	No
14	Cross-sectional	Buchanan, L. (1999)	5 adults	1 F/ 4 M	Range: (17-51)	Ceramic production and Pb glazing from Pb-acid batteries	Village of LaVictoria in Ecuador	DPOAE, ABR, & Pure-tone threshold	Mean BLL 41 μg/dL (range 19-56)	No	No
15	Cross-sectional	Wu, T. (2000)	220 workers	102 F/ 118 M	37 (sd=10)	Workers at two Pb-battery factories	Taiwan	Pure-tone thresholds	BLL as short-term and long-tenn value calculated from ambient Pb concentrations and years working at plant	LEQ for each indiv.	No
16	Cross-sectional	Counter, S. A. (2002)	30	15 F/ 15 M	median age =35 (17-55)	Pb glazing workers	Ecuador	Pure-tone thresholds. BAERs on 12 participants	BLL 45 (20=sd) μg/dL. Range of 11-80 μg/dL.	Reported in survey	No
17	Cross-sectional	Yokoyama, K. (2002)	29	all F	27 (22-29)	Pb glass factory workers (employed for 3-17 years, mean 8)	Beijing, China	BAEP	Mean BLL 56 μg/dL (range: 26-79)	No	No
18	Cross-sectional	Bleecker M. L. (2003)	359	all M	41 (sd=9)	Pb smelting workers. French and English speaking.	-	BAER	BLL, TWA from past 5 years, and integrated blood Pb measure - overtime working at plant.	No	No
19	Case-Control	Chuang, H.-Y. (2007)	121 HL/173 controls	all M	Cases 44 (sd=9)/ Controls 40 (sd=9)	Outpatients and occupational health examination workers with HL. Controls patients with no HL	Taiwan	Pure-tone thresholds	BLL geometric mean (11 μg/dL - cases / 4 μg/dL - controls)	Reported yes/no, if yes years of duration	Blood Mn, As, Se
20	Cross-sectional	Hwang, Y.-H. (2009)	412 total, 395 factory/17 admin.	I F / 411 M	36 (7=sd)	Steel workers	Taiwan	Pure-tone thresholds	BLL Grouped under 4 μg/dL, 4-7 μg/dL, and over 7 μg/dL	Groups <80, 80-85, and >85 dB	Mn, Cu, Zn, As, Cd

#	Type	First Author (Year)	N	Sex (F/M)	Mean Age	Pb Exposure Setting	Place	Hearing Test	Pb Measure	Noise	Metals
21	Cohort	Park, S. K. (2010)	448	all M	65 (7=sd)	Normative aging study-veterans	Eastern MA	Pure-tone thresholds	Bone (tibia and patella) Pb	Job title	No
22	Cohort	Choi, Y-H. (2012)	3698	1969 F/ 1729 M	42 (0.3=se)	NHANES-representative civilian US population	US	Pure-tone thresholds	BLL Geometric mean 1.54 (95 % CI: 1.49, 1.60) μg/dL	Fireanns, recreational, and job title	Cd
23	Cross-sectional	Saunders, J. E. (2013)	59	10 F/ 49 M	9 to 78	Artisanal gold miners	Nicaragua	Pure-tone thresholds, DPOAE	Finger nail (some toe) clippings. Median = 3.93 μg/g	Reported Low/ High	Hg, As, Mn, Al
24	Cross-sectional	Huh, D-A, (2016)	7596	4843 F/ 4115 M *	Range: 10-87	2010-2013 National Health Survey	Korea	Pure-tone thresholds	BLL – weighted geometric mean 2.08 μg/dL 95 % CI (2.05, 2.11)	Survey: Loud, occ., firearms	No

Table Abbreviations: ABR – auditory brainstem response (very similar to BAER); admin. – administration workers; ASM – age and sex matched; BAEP – brainstem auditory evoked potentials; BAER – brainstem auditory evoked response; BLL – blood lead levels; dB – decibels; DPOAE – distortion product otoacoustic emissions; F – female; Hz – hertz; indiv. – individual; LEQ – Equivalent Continuous Sound Level (measured in dB); Loud – loud noise group; M – male; MA – Massachusetts; μg/dL - micrograms Pb per deciliter blood; Occ. – occupational; Pb – lead; sd – standard deviation; se – standard error; TWA – time weighted average.

* Obtained from downloading available datafile.

TABLE 4.

Summary of Pb ototoxicity findings from twenty-four human study

PAPER	FINDINGS
Baloh, R. (1979)	• No significant differences between control and Pb group (baseline to study below).
Spivey, G. (1980)	• No significant changes from previous audiometric results (above) (Baloh et al. 1979) after 12 to 18 months of BLL monitoring and follow-up testing.
Holdstein, Y. (1986).	• Normal hearing threshold levels. • Significant difference between exposed and control IPL I-III with stimulus delivered at 10/s and 55/s. • A negative correlation between BLL and IPL for wave III-V was significant.
Lille, F. (1988)	• All BAEP results were found to be within normal ranges aside from one patient. • One Pb-exposed alcoholic participant was found to have an increased I-V interpeak latency of 4.7 ms.
Araki, S. (1992)	• Auditory ERP P300 component was prolonged significantly in Pb workers compared to control. • Auditory ERP P300 latency in Pb workers was correlated (Pearson's product moment correlation coefficient) significantly with BLL, UPb (not shown). • Controls had significantly lower BLL, plasma Zn, and plasma Cu.
Discalzi, G. L. (1992)	• No significant correlation for linear regression was found between 3-year BLL, BLL, or Pb exposure duration and BAEP latencies (I, III, and V). • All BAEP latencies and interpeak latency differences were significantly different in Pb workers compared to controls. • When comparing 21 Pb working participants with an average 3-year BLL above 50 μg/dL to 28 participants below 50 μg/dL, a significantly longer I-V interpeak latency was observed.
Discalzi, G. L. (1993).	• Greater I-V mean IPL between controls and workers. • Greater I-V mean IPL in workers with Pb levels over 50 μg/dL and those under 50 μg/dL.
Hirata, M. (1993).	• Latency of peak III-V was increased significantly in the Pb-exposed. • Latencies for individual peaks I and III were significantly longer in the unexposed workers.
Murata, K. (1993)	• All BAEP latencies (I, III, and V) were not significantly different between Pb workers and controls. • BAEP latency I-V and V were significantly correlated with packed cell volume in 20 workers. • Auditory ERP P300 latencies were significantly longer in Pb workers compared to controls. • Auditory ERP P300 latencies was significantly correlated (simple correlation coefficient) in 22 workers with BLL, urinary Pb, years of employment, urinary Zn, and age.
Murata, K. (1995)	• No significant differences in BAEP latencies (I, I-III, or I-V) were found between Pb workers and controls.
Farahat T. M. (1997).	• 8 kHz was significantly different between workers with BLL < 30 μg/dL and those ≥ 30 μg/dL. • Threshold at 2, 4, and 8 kHz were significantly different in workers and controls. • A significant positive correlation was observed at 8 kHz between BLL and threshold.
Forst, L. S., (1997)	• High frequency HL was evident in cohort. • Significant Spearman correlation with threshold and BLL at 4 kHz. • Trend tests were not significant.
Fujimura, Y. (1998)	• BAEP latency V was significantly different than expected values for Pb smelter #1. • Auditory ERP P300 latency was significantly different from control for Pb smelter #1.
Buchanan, L. (1999)	• Two of five participants reported noise exposure histories. One participant with history of noise exposure had thresholds of 110 dB at 6 kHz in one ear. • Range of mean hearing thresholds were 9.5 dB at 2 kHZ to 32 dB at 6 kHz. • At high frequencies mean DPOAE amplitudes show lowered levels consistent with noise exposure. • No significant associations between DPOAE and BLLs were observed.
Wu, T. (2000)	• Age was correlated with HL. • Long-term Pb exposure metric was significantly associated with HL, though correlated with age. • Increasing thresholds were noted when groups were stratified by BLL (25-40, 41-60, and over 60 μg/dL); however the lowest group (below 25 μg/dL) did not fit this relationship.
Counter, S. A. (2002)	• More HL in men than women. • Four case profiles with high Pb levels described. • No significant relationship between BLL and thresholds. • Those with hearing loss displayed longer (non-significant) absolute wave latencies, but normal IPL.
Yokoyama K. (2002)	• No significant differences between Pb workers and controls were observed in BAEP latencies (I, I-III, and III-V). • BAEP latencies were not found to correlate with BLLs.
Bleecker M. L. (2003)	• Peak I & V latency significantly correlated with Integrated Pb exposure, BLL and TWA. • Peak III latency correlated significantly only with TWA, and integrated Pb exposure.

PAPER	FINDINGS
	• When stratifying by BAEP pathology, the group with longest wave I latency and I-V IPL had significantly higher BLL and TWA than the group with normal wave I latency and normal I-V IPL.
Chuang H.-Y. (2007)	• Age was associated with HL. • Increasing selenium levels were protective against HL. • An increase of 0.1 μg/dL of log-transformed BLL significantly associated with a 7 dB increase in HL.
Hwang, Y.-H. (2009)	• Higher BLLs increased risk of HL in high frequencies of 3, 4, 6, and 8 kHz. • Higher BLLs were significantly correlated with hearing loss at 0.5, 2, 3, 4, 6, and 8 kHz as well as the average noise and maximum noise levels. • Levels above 7 μg/dL were significantly associated with hearing thresholds above 25 dB (odds ratios 3.06–6.26) in logistic models adjusting for noise and age.
Park, S. K. (2010)	• Odds of HL significantly increased with bone (patella) Pb levels. • A positive interaction was found between bone (tibia) Pb levels and time in the linear mixed effects model showing a faster elevation of thresholds with increasing levels of Pb. • Effect modification analysis showed non-linear dose-response for threshold changes and low, medium, and high occupational noise.
Choi, Y-H. (2012)	• Age-adjusted BLLs were higher in participants who were older, less-educated, smokers, those with high occupational noise exposures, those with a BMI over 30, and those without diabetes. • Participants with HL had significantly higher age-adjusted geometric mean BLL (0.46 to 0.40 μg/dL). • BLL were significantly correlated with blood cadmium levels. • Highest BLL quintiles had 18.6 % (95 % CI: 7.4, 31.1 %) higher average thresholds than those in the lowest quintiles. • Models showed the average thresholds trended across all quintiles significantly with BLL before and after adjusting for occupational and recreational noise exposures. • In logistic models (using a yes or no for hearing loss defined as an average of thresholds at four frequencies over 25 dB) BLL was found as a significant predictor of HL, however it was no longer significant when noise exposure was adjusted for.
Saunders, J. E. (2013)	• No meaningful significant relationships found in the group as a whole after Bonferroni corrections. • DPOAE at 3 kHz, 4 kHz, and the mean of all DPOAE frequencies were significantly correlated with BLL before Bonferroni corrections. • Three case reports of workers with high metals exposure and hearing loss.
Huh, D-A, (2016)	• Risk of hearing loss (defined as pure-tone average at or over 25 dB) increased for participants with BLLs above the mean OR = 1.14 (95 % CI: 0.42, 3.13). • Increasing levels of Pb significantly trended with increasing hearing loss in a fully adjusted model – controlling for age, sex, smoking status, monthly income, education levels, body mass index, occupational noise exposure, loud noise exposure, firearm noise exposure, hypertension, and diabetes mellitus. A 43 % higher odds of hearing loss (95 % CI: 1.03–2.00) was shown in this model for every 1 μg/dL increase in BLL. • The highest quintile of BLL (2.9–26.5 μg/dL) showed significant increased risk for hearing loss across two other models adjusting for fewer variables. However the trend across quintiles in these other models was not significant.

Table Abbreviations: BLL – blood lead levels; CI – confidence interval; HL – hearing loss; IPL – interpeak latency; OR – odds ratio; Pb – lead; TWA – time weighted average.