The Noise Manual

Sixth Edition

Disclaimer

The American Industrial Hygiene Association (AIHA®), as publisher, and the authors have been diligent in ensuring that the material and methods addressed in this book reflect prevailing toxicology, and occupational health and safety and industrial hygiene practices. It is possible, however, that certain procedures discussed will require modification because of changing federal, state, and local regulations, or heretofore unknown developments in research.

AIHA and the editors and authors disclaim any liability, loss, or risk resulting directly or indirectly from the use of the practices and/or theories discussed in this book. Moreover, it is the reader's responsibility to stay informed of any changing federal, state, or local regulations that might affect the material contained herein, and the policies adopted specifically in the reader's workplace.

Specific mention of manufacturers and products in this book does not represent an endorsement by AIHA®.

Stock Number: ENOM22-619
ISBN: 978-1-950286-07-2

HEALTHIER WORKPLACES | A HEALTHIER WORLD

AIHA
3141 Fairview Park Drive, Suite 777
Falls Church, VA 22042
Tel: (703) 849-8888
E-mail: Infonet@aiha.org
aiha.org

Printed in the United States of America

The Noise Manual, 6th edition, edited by
D.K. Meinke, E.H. Berger, R.L. Neitzel, D.P. Driscoll, and K. Bright
Chapter 7: Ototoxicity and Otoprotection: Complex Interactions Between Noise and Chemicals, pp. 123–151

Chapter 7: Ototoxicity and Otoprotection: Complex Interactions Between Noise and Chemicals

7

By Thais C. Morata, Colleen G. Le Prell, Chris Spankovich, and Adrian Fuente

"Everything is complicated; if that were not so, life and poetry and everything else would be a bore."

—Wallace Stevens

Contents

Introduction to Ototoxicity and Otoprotection

Sound energy results from molecules vibrating and moving in waves within a medium such as air or water; sound does not exist in a vacuum. That excessive sound (noise) can injure the ear directly via mechanical damage and indirectly through metabolic stress is clear. Recently, it has become evident that exposure to chemicals can also be harmful, in part due to metabolic stress related to chemical exposure.

To prevent noise-induced hearing loss (NIHL), reducing noise at its source, decreasing the duration of exposure, and/or using hearing protection devices (HPDs) are accepted strategies needed for protection of our hearing. However, we now know that death of the sensory cells in the inner ear happens not only from exposure to noise, but also from exposure to chemicals and from intake of ototoxic drugs. *In addition to the potentially hazardous effects of any one of these three insults, there are synergistic effects of noise, chemicals, and ototoxic drugs.* Cell death and hearing loss from noise and/or chemicals are now thought to be at least, in part, a consequence of metabolic stress that results in toxic accumulation of free radicals. Scientific investigations have demonstrated that free radical scavengers ("antioxidants") and agents that enhance the natural antioxidant systems can attenuate the harmful effects of noise or chemicals (or the combination of noise plus chemicals) on the inner ear.

These developments represent a departure from traditional noise research, which was characterized by the study of noise as if it occurred alone in the environment. Exposure standards and recommendations assume that the health effects of combined exposure to two substances can be predicted by adding the adverse effects resulting from exposures to each individual substance. In contrast to these assumptions about additive effects across insults, recent investigations have revealed synergistic effects during mixed exposures. The study of multiple exposures in relation to each other is not new, but the literature has

been limited given the complexity inherent in multivariate interactions. This chapter examines interactions that damage the ear through increasing ototoxicity or protect the ear via a mechanism termed "otoprotection." The chapter concludes with a public health proposal for widening the framework of hearing loss prevention initiatives.

Ototoxicity and Noise Interactions

The potential ototoxicity of certain therapeutic drugs has been recognized since the 19th century. Schacht and Hawkins (2006) reviewed early reports that associated intake of certain drugs such as quinine and acetylsalicylic acid with temporary hearing loss, dizziness, and tinnitus. Many well-known ototoxic drugs continue to be used in clinical situations, as they are necessary to treat serious and sometimes life-threatening conditions (for recent review, see Campbell and Le Prell, 2012). The prescription of these drugs may trigger "ototoxicity monitoring" of patients to allow early detection of auditory effects and, when necessary, audiologic interventions to address the hearing impairment (American Academy of Audiology, 2009).

In contrast to drug ototoxicity, only in the past 25 years has the ototoxicity of chemicals become a concern for researchers, toxicologists, audiologists, and other healthcare professionals. Initial reports described the ototoxicity of environmental chemicals after acute intoxications or poisonings and included observations that hearing loss was more common and sometimes more severe in work settings where chemical exposures occurred (Barregård and Axelsson, 1984). Since then, there has been considerable progress toward understanding the effects of certain environmental and occupational chemicals on the auditory system and their interactions with noise (Fechter et al., 1987; Morata, 1989; Lataye et al., 2000). Today, ototoxic properties have been identified for multiple classes of industrial chemicals, including solvents, fuels, metals, asphyxiants, pesticides, and polychlorinated biphenyls (PCBs) (for review, see Johnson and Morata, 2010).

Among the environmental/occupational chemicals, solvents and carbon monoxide are the most extensively studied to date because of their wide use in several industrial sectors. Studies conducted with animal subjects have shown that some solvents can reach the inner ear through the blood stream even before they are metabolized. Solvents were found in the endolymph and perilymph, causing damage to some inner ear structures and also impairing auditory function (Campo et al., 1999). Toluene, styrene, solvent mixtures, lead, and carbon monoxide (the latter only in combination with noise) have been shown to be ototoxic (Johnson and Morata, 2010). For these substances, the number of existing studies is relatively large. Comprehensive approaches have been taken in investigating their ototoxicity (testing of different exposure parameters and combinations of agents, attempting benchmark dose calculations, testing of hypotheses for the inhibition of the observed effects). Other chemicals that have been studied in less detail with respect to ototoxicity include xylenes, ethylbenzene, chlorobenzene, trichloroethylene, *n*-hexane, *n*-heptane, carbon disulphide, mercury, organotins, hydrogen cyanide, acrylonitrile, 3,3′-iminodipropionitrile (IDPN), pesticides, and PCBs. For an extensive review of the studied chemicals and details on the experiments, see Johnson and Morata (2010; available online at http://hdl.handle.net/2077/23240) and the report of the European Agency for Safety and Health at Work, 2009 (https://osha.europa.eu/en/publications/combined-exposure-noise-and-ototoxic-substances/view).

KEY CONCEPT: Ototoxicants may interact with each other and with noise when exposure is combined (simultaneously or sequentially), and various types of interaction have been observed.

A synergistic effect has been described for solvents and noise; that is, the effect of the combined exposure is more detrimental than the simple sum of the individual effects. In 2014, Campo et al. described that the hazardous effects of impulse noise exposure were enhanced by styrene exposure. The authors argued that the pharmacological toxic effects of the solvents might explain the findings. Thus, styrene, like toluene and other aromatic solvents, could have two distinct effects: a cochleotoxic effect, which is observed in the cochlea after a long incubation period (Campo et al., 2001), and a rapid neurotoxic impact on the central nervous system (Venet et al., 2011). A disturbance of the protective acoustic reflex could allow a hazardous higher acoustic energy to penetrate the inner ear (Campo et al., 2007, 2014; Maguin et al., 2009), which could make a co-exposure more dangerous than a single exposure to noise or to styrene. Recent data suggest the synergistic toxicity of noise and styrene, with greater damage following exposure to impulsive noise (Campo et al., 2014). The onset, site, mechanism, and extent of ototoxic damage of these toxicants vary according to risk factors that include type of chemical, level and duration of chemical exposure, interactions between chemicals and noise, noise exposure level, and duration (Johnson and Morata, 2010).

A different "greater than additive" scenario has been reported for carbon monoxide and noise. In experimental animals, carbon monoxide has not been associated with ototoxicity *unless* the exposure is combined with noise. When the exposures are combined, carbon monoxide will potentiate the effects of noise at noise exposure conditions that have limited effects on auditory function (Young et al., 1987; Fechter et al., 1988). During intermittent noise exposure with long quiet periods, carbon monoxide exposure may produce unexpectedly large permanent threshold shifts (Chen et al., 1999; Rao and Fechter, 2000b). However, when carbon monoxide was absent, hearing loss was reduced, presumably due to the quiet breaks. Thus, the data did not

validate the anticipated relationship between percentage of time noise is present (noise duty cycle) and hearing loss. Instead, the mildest noise duty cycle (noise exposure interrupted with quiet breaks) produced maximal hearing loss only when carbon monoxide was also present.

Table 7.1 summarizes key descriptors of the effects of ototoxicants found in the workplace and investigated to date. Table 7.2 lists the studied ototoxicants by class, the type of possible interaction with noise, and sources of exposure (adapted from Johnson and Morata, 2010).

It is important to remember that exposures to these chemicals can occur outside the work environment, just as with noise. Nonoccupational exposure can happen from any activities that involve solvents, paint, polyurethanes, paint thinners, degreasers, and fuels.

Audiological Features of the Effects of Solvents on the Auditory System

Solvents affect not only the cochlea, as noise does, but also the central auditory structures (for review, see Prasher et al., 2002; Hodgkinson and Prasher, 2006). These adverse auditory effects of solvents may be due to a combination of oto- and neurotoxicity (Morata and Lemasters, 1995). Ototoxicity induces outer hair cell (OHC) dysfunction in the cochlea (similar to the effects of noise), whereas neurotoxicity induces central auditory dysfunction.

The main audiological sign of ototoxicity is hearing loss, i.e., thresholds poorer than expected, relative to age. Audiological signs of neurotoxicity may or may not include hearing loss, but individuals exhibit difficulty discriminating between signals, such as speech sounds. Thus, it has been recommended that the effects of solvents on the auditory system, either alone or when combined with noise, should be evaluated using a test battery approach (Sliwinska-Kowalska et al., 2007; Zamyslowska-Szmytke et al., 2009). Currently, in the United States and other countries, noise-exposed workers are monitored using conventional pure-tone air conduction audiometry. This limited testing to assess auditory function in solvent-exposed workers with or without noise exposure may be inadequate, as solvents affect more complex measures of perception rather than simply compromising sound detection sensitivity.

Animal Studies: Cochlear (Peripheral) and Central Auditory Dysfunction

Research using animal models has demonstrated that organic solvents such as toluene, styrene, xylene, and ethyl benzene induce damage to the outer hair cells in the cochlea (Sullivan et al., 1988; Johnson and Canlon, 1994; Campo et al., 1997; Cappaert et al., 1999, 2000; Loquet et al., 1999; McWilliams et al., 2000). The damage caused by solvents is first observed in the third row of outer hair cells; hair cell loss progresses toward the second and first rows as damage accrues. Outer hair cell function can be assessed in humans and animals using otoacoustic emission (OAE) tests, but OAE tests are not currently required as part of federally mandated occupational hearing conservation programs.

Rats that were simultaneously exposed to both toluene and noise suffered a more severe hearing loss than predicted based on summated hearing loss from equivalent exposure levels of each agent alone (Lataye and Campo, 1997; Brandt-Lassen et al., 2000). Such effects may be mediated centrally, given that toluene inhibits the acetylcholine (ACh) receptors located in the efferent auditory system (medial olivocochlear bundle), which mediate outer hair cell contraction in the cochleae (Lataye et al., 2007). Toluene may similarly inhibit the ACh receptors of the

Table 7.1 — General descriptors of ototoxic effects of chemicals found in the environment from animal experiments and from clinical and field studies

Descriptors of Ototoxic Effects of Chemicals from Animal Experiments
• Cochlear lesion is primary effect • Effects are greatest in the mid-frequency audiometric range • Effects observed in rats, mice, guinea pigs, and monkeys • Ototoxicity observed after exposure to solvents, metals, or insecticides in absence of noise • Ototoxicity after carbon monoxide, hydrogen cyanide, or acrylonitrile exposure observed in combination with noise • Additive ototoxic effect between solvents (with noise exposure controlled)
Descriptors of Ototoxic Effects of Chemicals from Clinical and Field Studies
• Occupational/environmental exposure to chemicals (via contaminated water, food, or air, including dust) can affect auditory system • Auditory effects reported following intentional inhalation or accidental poisoning • Auditory effects reported following acute exposure or long-term, low-dose chronic exposure • Increased prevalence of hearing loss in pure-tone audiograms (mild to moderate, bilateral, audiometric loss; high-frequency notch configuration common, but mid-frequencies can also be affected) • Interaction with noise not clearly identified as synergistic or additive due to limitations in exposure history ascertainment • Synergism demonstrated for styrene and toluene • Cochlear and retrocochlear or central lesion sites lead to poorer than expected performance on tests that evaluate more central portions of auditory system

Table 7.2 — Substances with ototoxic properties, their interaction with noise, and possible sources of exposure

Substance	Interaction with noise	Industrial uses http://hazmap.nlm.nih.gov/
Solvents		
Styrene	Synergism	Manufacture of synthetic rubber, fiberglass-reinforced polyester products. Part of floor waxes, polishes, paints, adhesives, metal cleaners, and varnishes.
Toluene	Synergism	One of the 50 most commonly produced industrial chemicals. Solvent carrier in paints, thinners, adhesives, inks, glues, enamels, and a component of gasoline. Production, handling, and use of toluene and toluene-containing products, e.g., chemical laboratory workers, gasoline blenders, lacquer workers, paint and paint thinner makers, petrochemical workers, maintenance workers, painters, and printers.
Xylenes	No data	Present in motor and aviation fuel but also used as a solvent in the paint, printing, rubber, and leather industries.
Trichloroethylene (TCE)	Synergism	Degreaser in metal cleaning operations and in textile cleaning. Also used as a paint stripper, adhesive solvent, ingredient in paints and varnishes, and in the manufacture of organic chemicals.
Ethylbenzene	Additive/synergism	Unusual in the work environment. As part of mixed xylenes, ethylbenzene is one of many solvents in solvent mixtures (paints and lacquers and in rubber and chemical manufacturing industries).
Chlorobenzene	No data	Raw material in chemical synthesis, as a solvent and detergent.
n-Hexane	No data	Production of tires, in glues for the manufacture of leather products and textiles, as a raw material in the production of other chemicals, and as an additive to gasoline.
n-Heptane	No data	Anesthetic, solvent, organic synthesis, preparation of laboratory reagents.
Carbon Disulphide	No data for potentiation	Manufacture of regenerated cellulose rayon (by the viscose process) and cellophane, carbon tetrachloride, the vulcanization and manufacture of rubber and rubber accessories, the production of resins, xanthates, thiocyanates, plywood adhesives, flotation agents, solvent and spinning-solution applications, conversion and processing of hydrocarbons, petroleum-well cleaning, brightening of precious metals in electroplating, rust removal from metals, removal and recovery of metals and other elements from wastewater and other media, in refining petroleum jelly and paraffin, and in extracting oil from bones, olives, and rags.
Solvent Mixture (jet fuel or white spirit)	Additive/synergism	All of the above, plus handling of fuels.
Metals		
Lead	Additive	Manufacture of car batteries, sheet metal, pipes, and foil, in mining and in polluted environments. Individuals employed in any of these occupations may bring lead dust on their bodies or clothing into their homes.
Mercury	No data	Present in contaminated air, water, and food, or through the skin. Workers may be exposed to mercury and its compounds in mercury mines and refineries, chemical manufacturing, fluorescent light bulb manufacturing, dental/health fields, fossil fuel power plants, and metal smeltering.
Organotins or Trimethyltins	No data	Production of plastics in the chemical industry and as biocides in antifouling boat bottom paints.

Table 7.2 — Substances with ototoxic properties, their interaction with noise, and possible sources of exposure (cont.)

Substance	Interaction with noise	Industrial uses http://hazmap.nlm.nih.gov/
Systemic Asphyxiants		
Carbon Monoxide	Potentiation	Common contaminant. Product of incomplete combustion of fuels, coal, oil, and wood, also present in gasoline-powered engine exhaust and tobacco smoke. Forging, melting, pouring and welding metals, in farm operations, firefighting, sewage and water treatment jobs.
Hydrogen Cyanide	Potentiation	Production of acrylic resin plastic and other organic chemical products, tempering steel, dyeing, explosives, and engraving. Present in vehicle exhaust, tobacco smoke, and the smoke of burning nitrogen-containing plastics.
Acrylonitrile	Potentiation	Production of other chemicals such as plastics, synthetic rubber, and acrylic fibers. It is one of the 50 most commonly produced industrial chemicals.
3,3´-Iminodipropionitrilem (IDPN)	No data	No reports on occupational exposures to and no occupational exposure limits (OELs) for IDPN were located.
Pesticides	No data	Herbicides, insecticides, fungicides, and fumigants.
Polychlorinated Biphenyls (PCBs)	No data	Repair and maintenance of PCB transformers, accidents, fires, or spills involving PCB transformers and older computers and instruments, and disposal of PCB materials. Caulking materials, elastic sealants, and heat insulation have also been known to contain PCBs.

efferent motor neurons located near the facial nerve nuclei that mediate the middle ear muscle systems (Lataye et al., 2007; Venet et al., 2015). The region where the cell damage occurs in the auditory system caused by another ototoxic solvent, styrene, was shown to depend on the associated noise spectrum (Venet et al., 2015).

Human Studies: Evidence of the Adverse Effects of Solvents on Pure-Tone Audiometric Thresholds

Several studies have utilized pure-tone audiometry to investigate the hearing thresholds of solvent-exposed workers, as this test is often used for monitoring hearing in industry. Hearing loss induced by solvents has been found in workers exposed to mixtures of toluene, ethyl acetate and ethanol (Morata et al., 1997a), and xylene and ethyl acetate (Sliwinska-Kowalska et al., 2001). Sliwinska-Kowalska et al. (2001) reported hearing loss in 30% of workers exposed to organic solvents, 20% of noise-exposed subjects, and 6% of non-exposed subjects. The relative risk value for hearing loss in workers exposed to solvents was greater (9.6) than that for workers exposed only to noise (4.2). Sulkowski et al. (2002) reported high-frequency sensorineural hearing loss in 42% of workers exposed to a mixture of solvents in contrast to just 5% among the control subjects. Morata et al. (2002) reported an additive damage effect of styrene for pure-tone thresholds at 2, 3, 4 and 6 kHz. The odds ratio for hearing loss estimated by Morata et al. (2002) was 2.44 times greater for each increment of 1 mmol of mandelic acid (a biologic marker of styrene exposure) per gram of creatinine in urine, leading to the conclusion that styrene, even below recommended limits, has a toxic effect on the auditory system. Sliwinska-Kowalska et al. (2003) similarly detected a four-fold increase in the odds of developing hearing loss in subjects exposed to styrene. A positive linear relationship was observed between average working life exposure to styrene concentrations and hearing thresholds at 6 and 8 kHz. In summary, the configuration of the mean audiometric results may look the same for workers exposed to noise and those exposed to solvents, but the thresholds can be poorer in frequencies that are usually not as affected by noise, such as 2, 3, and 8 kHz.

Human Studies: Evidence of the Adverse Effects of Solvents on Central Auditory Functions

Environmental/occupational chemicals may affect the central auditory system, including auditory nerve and/or auditory centers in the brain. Studies utilizing electrophysiological techniques have also been conducted in workers exposed to solvents. Workers exposed to toluene had poorer auditory brainstem response results than a non-exposed group of workers matched for gender and age (Abbate et al., 1993). Additional evidence of solvent-induced central auditory dysfunction in humans comes from Vrca et al. (1996) and Hirata et al. (1992). The P300 (a long laten-

cy auditory evoked potential) is also affected by solvent exposure in workers (Steinhauer et al., 1997; Moen et al., 1999). More recently, Draper and Bamiou (2009) presented a case study of a person exposed to xylene who presented with auditory neuropathy, as evidenced by abnormal auditory brainstem response results and presence of OAEs.

If solvent exposure produces peripheral and/or central auditory dysfunction, the impact of hearing loss on the worker's daily life may be pronounced. Not only will sounds be perceived as quieter, but they may also be perceived as distorted. Word recognition may be compromised, particularly in background noise, making it difficult, for instance, to hold a conversation in a busy restaurant or at a party. Dysfunction of the auditory system in workers exposed to a mixture of solvents has been detected by many investigators using behavioral tests (Ödkvist et al., 1987, 1992; Pollastrini et al., 1994; Laukli and Hansen, 1995; Niklasson et al., 1998; Varney et al., 1998; Moen et al., 1999; Fuente and McPherson, 2007). Fuente and McPherson (2007), for example, found that workers exposed to a mixture of solvents (toluene, xylene, and methyl ethyl ketone) had abnormal results on behavioral central auditory processing tests, suggesting auditory processing disorders. The authors suggested that solvents may affect sound detection despite normal hearing thresholds.

KEY CONCEPT: Taken together, hearing-related functions such as sound discrimination and sound localization may be affected among workers exposed to ototoxicants, and tests that evaluate the full impact of the ototoxicant on the auditory system, from the cochlea to higher auditory centers, are needed. Questionnaire-based data on speech recognition difficulties or other auditory problems may help identify other subtle effects of chemicals or noise on the auditory system and may serve as a screening tool for more advanced diagnostic testing. Comparisons of the prevalence of hearing disorders among groups with different noise/chemical exposure conditions may also allow negative exposure effects to be identified based on calculated risk ratios.

Conditions and Exposure Parameters Associated with Ototoxicity of Occupational Chemicals

The minimum concentration and duration of exposure to various chemicals to produce an auditory effect has not been established in humans. The lowest observed adverse effect level (LOAEL) and no-observed adverse effect level (NOAEL) have been identified in animal experiments for several substances (Johnson and Morata, 2010). Interactions between agents indicate that exposure to one agent could modify the LOAEL and NOAEL of the other agent. For example, a single exposure to a particular chemical in quiet may not elicit a toxic response, and a given noise exposure may not be harmful on its own. However, the same chemical exposure in the presence of that otherwise "safe" noise can result in hearing loss even though neither the chemical nor the noise were harmful on their own. These interactions have been shown in animal models (Fechter et al., 2007; Chen and Henderson, 2009), and it appears that the interaction effect may vary with the specific type of noise insult (Lund and Kristiansen, 2008) and the chemical level (Mäkitie et al., 2003). Interaction effects have also been shown in workers (Kim et al., 2005; Chang et al., 2006; El-Shazly, 2006; Mohammadi et al., 2010; Metwally et al., 2012; Pawlaczyk-Luszczynska et al., 2012), although some studies have not detected these interaction effects at lower levels of chemical exposure (Schäper et al., 2008; Vyskocil et al., 2008a, 2008b). Across studies, there appears to be a difference in LOAEL in humans and experimental animals, with the LOAEL being lower in humans than in animals (suggesting greater risk in humans, see Johnson and Morata, 2010). All efforts to measure LOAELs in humans are complicated by the fact that human exposure concentration is often unknown and interaction factors are unknown as well. What is clear is that cases of hearing loss have been observed after chemical exposures that were within permissible limits.

KEY CONCEPT: Controversial Point. The lowest level necessary for solvents to affect the auditory systems of humans and experimental animals is very different. In the investigations with experimental animals, high concentrations of solvents were used for short intervals of time, in contrast to significantly longer duration of exposure (in years) to significantly lower concentration for many workers. Yet both types of studies have reported on the association of solvent exposure and hearing effects. This discrepancy in exposure has raised questions on the extrapolation of animal experiment results to occupational exposure conditions. Safety factors are used to account for uncertainties related to interspecies extrapolation, extrapolation from acute to chronic exposure, limitations in numbers of subjects tested, and having limited data concerning dose-effects (Faustman and Omenn, 1996). As there is no basis for determining whether or not humans and rodents differ in terms of sensitivity to solvents and noise, some researchers have used values based on other health outcomes (Fechter, 2004). It has been demonstrated, however, in studies with experimental animals, that by adding other stressors such as impact noise and carbon monoxide or ensuring that the animals are active during solvent exposure, the lowest level of solvent exposure needed to elicit an auditory effect was much reduced (Lataye et al., 2005). The auditory effects of solvents may have been observed at lower concentrations in humans as they are generally exposed to solvents in combination with a multitude of other factors

(several exposures, physical demands, etc.), whereas animal experiments typically involve isolated solvent exposures. Another complication in determining the concentration needed for a hearing loss to occur in humans exists because often individuals are not aware of the concentration they have been exposed to and many factors can interact in causing a hearing loss.

Until now, few human studies have examined the time course of exposure over which chemical exposures first begin to affect the human auditory system, and there is still uncertainty regarding whether chemical solvent ototoxicity is a chronic or acute process. The investigations that have examined the effects of solvents over time generally indicate that hearing loss can be observed two to three years earlier than is usually seen with noise exposure (Morata et al., 1993, 1997a, 1997b). Other data suggest a longer time course, however, with a significant effect of solvents on hearing after five or more years of chemical exposure (Jacobsen et al., 1993). This issue of time course and onset of deficits depends on the ototoxicant and other characteristics of the exposure, and further investigation is needed. Indeed, a major challenge in this area is that the number of chemicals studied to date is very small, particularly when one considers the enormous number of existing industrial chemicals and the thousands of new chemicals placed on the market every year. It is critical to better identify the mechanisms through which chemicals (and noise) affect the auditory system. One mechanism of trauma common to the physical agent (noise) and some of the ototoxic chemicals is oxidative stress. Combinations of non-damaging noise and oxidizing chemical agents have been suggested to lead to oxidative stress that causes the death of hair cells in the inner ear (McWilliams et al., 2000; Pouyatos et al., 2005), and these damaging effects can be reduced by antioxidants (Fechter, 2004). The antioxidant *N*-acetylcysteine (NAC) has reduced styrene ototoxicity (Yang et al., 2009), and yielded protection against liver toxicity induced by styrene (Meszka-Jordan et al., 2009). The mechanisms for damage and protection are discussed in the next section.

Oxidative Stress: A Common Mechanism for Damage by Noise or Ototoxicants

The most common elements in the human body are carbon, hydrogen, nitrogen, oxygen, calcium, and phosphorus. These elements combine to form different molecules. Most molecules found in living organisms (in vivo) are stable. However, there are many molecules that have unpaired electrons, and these belong to the broad category of "free radicals" (Halliwell and Gutteridge, 2007). The unpaired electron makes the molecules electrically charged and thus the charged molecule seeks to bind to another charged molecule to stabilize the electrical charge. To become stable, a given molecule might "donate" its unpaired electron to another less stable molecule (a process called oxidation), or it might have an electron donated to it by another less stable molecule (a process termed reduction). The reactions through which these charged molecules break apart and rebind, to form new molecules after the transfer of electrons, are termed oxidation-reduction (or redox) reactions. The oxidized molecule loses an electron, while the reduced molecule gains an electron. Readers are referred to Campbell (2003) for a more complete list of oxidative-stress terms and concepts and their definitions, written specifically for audiologists.

There is an enormous amount of literature on intracellular free radical formation and its biological effects. Three of the major oxygen-based free radical species are the superoxide radical (O_2-), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($OH^{\cdot}$); approximately 1–3% of the oxygen consumed by the body is converted into one of these reactive molecules during normal cell energy metabolism (see Seifried et al., 2007). Superoxide, hydrogen peroxide, and hydroxyl radicals are termed reactive oxygen species (ROS). Reactive molecules that are derived from nitric oxide (NO) are termed reactive nitrogen species (RNS), and the best understood reaction is that of nitric oxide and superoxide, which produces highly toxic peroxynitrite (ONOO-) (Patel et al., 1999). At normal physiological levels, these free radicals play a key role in normal cell physiology; they assist the immune system, mediate signal transduction/cell signaling, and drive apoptotic (programmed) cell death (Seifried et al., 2007). The balance between free radical production and endogenous scavenging is critical, however, as accumulated free radicals can damage cells.

Lim and Melnick (1971) were among the first to propose that intense metabolic activity (and corresponding oxidative stress) might contribute to noise-induced inner ear pathology. Empirical evidence was slow to emerge; it was not until the mid-1990s that Yamane et al. (1995) explicitly demonstrated noise-induced superoxide production in the stria vascularis. These data were extended by Ohlemiller et al. (1999), who reported noise-induced hydroxyl radical formation. Since then, multiple free radicals have been explicitly localized to outer hair cells (Nicotera et al., 1999; Ohinata et al., 2000; Yamashita et al., 2004, 2005; Henderson et al., 2006; Du et al., 2011), lateral wall and/or stria vascularis (Ohinata et al., 2000; Shi and Nuttall, 2003; Heinrich et al., 2008), and supporting cells (Ohinata et al., 2000; Yamashita et al., 2004; 2005; Du et al., 2011). Accumulation of free radicals leads to cell death in the inner ear, and antioxidant therapies can prevent cell death and accompanying NIHL (for reviews, see Le Prell et al., 2007b; Abi-Hachem et al., 2010; Poirrier et al., 2010; Le Prell and Bao, 2012). A similar literature on free radical formation after chemical insult is slowly emerging. Carbon monoxide (Rao and Fechter, 2000a) and hydrogen cyanide (Fechter et al., 2002) may potentiate NIHL through

generation of ROS during combined exposures. Rabinowitz et al. (2002) suggested that antioxidants may play a protective role in humans against hair cell damage due to noise or aging.

Endogenous Defense Against Oxidative Stress

Several endogenous substances reduce highly toxic free radicals to less toxic free radicals and further reduce these less toxic molecules to nontoxic molecules that can be safely excreted. The primary endogenous antioxidant defense is provided by superoxide dismutase (SOD), catalase, and glutathione (GSH) (for review, see Campbell and Le Prell, 2012; Le Prell and Bao, 2012). Production of these endogenous substances is mediated by genetic polymorphisms; these are two or more discontinuous genetic variants found in a population in such proportions that they cannot be maintained simply by mutation but rather are traced through specific inheritance patterns.

Genetic polymorphisms that mediate production of SOD, catalase, GSH, and related enzymes appear to mediate vulnerability to noise in both animal and human populations. Given the growing availability and decreasing cost of genetic screening tools, it is increasingly possible to imagine genetic testing to assess NIHL vulnerability based on the presence (or absence) of genetic polymorphisms in human workers. Indeed, the addition of routine genetic testing to newborn hearing screening programs has already been advocated to allow infants with subclinical hearing loss and infants that do not have hearing loss at birth but who are likely to develop prelingual hearing loss to be identified (Morton and Nance, 2006). Although screening for genes that mediate vulnerability to noise might seem logical from a hearing conservation perspective, there are obvious obstacles to mandatory testing. Some issues include who has access to genetic data, what safeguards can be put in place to assure data are not used to influence access to or cost of health insurance, and how "unexpected" results are dealt with (see, for example, Arnos, 2008; Beskow et al., 2011; Cadigan et al., 2011; Christenhusz et al., 2012). These issues fall outside the scope of this chapter, but they do merit attention.

Therapeutic Interventions to Attenuate Oxidative Stress

KEY CONCEPT: Special Consideration. There are no FDA-approved products for prevention of hearing loss. A variety of dietary supplements are marketed for the purpose of maintaining hearing function, but all carry disclaimers and caution is required. We do not know what agents will be effective for human patients or what an effective dose will be. Multiple therapeutics are being investigated.

The possible protection of the inner ear against different ototraumatic agents using "exogenous" therapeutics has been well studied in animal models (for review see Le Prell and Bao, 2012), and potential protective agents have been assessed in clinical trials (for review see Le Prell and Lobarinas, 2015). A summary of several agents is shown in Table 7.3. These agents have been the subject of recent detailed reviews, with respect to animal data (Abi-Hachem et al., 2010; Poirrier et al., 2010; Le Prell and Bao, 2012), epidemiological data (Le Prell and Spankovich, 2013; Spankovich and Le Prell, 2013, 2014), and clinical investigation (Le Prell and Lobarinas, 2015). Here, brief summaries of the mechanisms of action and key data to date are provided, along with a statement on the current status of the testing for each agent and information related to safety. *As of the time this chapter was prepared, there are no agents approved by the U.S. FDA for the prevention of hearing loss, including NIHL.* Relevant to SOD and catalase supplements (above) and all agents in the following section, readers are cautioned to be aware of potential interactions with prescribed drugs (Webb, 2007; Boullata and Hudson, 2012), issues influencing bioavailability (Espin et al., 2007; Holst and Williamson, 2008; Guo and Bruno, 2015; McClements et al., 2015), and safety of over-the-counter agents (Consumer Reports, 2004; Basch et al., 2005; Webb, 2007; Consumer Reports, 2010; Finley et al., 2014).

The Healthy Eating Index

Combinations of nutrients have been shown to have synergistic benefit in studies outside the auditory system (see, for example, Yeum et al., 2009). A synergistic interaction among vitamins A, C, E, and magnesium was explicitly shown by Le Prell et al. (2007a) in their evaluation of NIHL in the guinea pig, and epidemiological data suggest the potential for synergistic interactions in humans as well (Choi et al., 2014b). A critical question is whether protection will translate to human subjects as a function of diet, supplement use, or both. Data regarding effects of diet on human hearing are extremely limited (Le Prell and Spankovich, 2013). Although the benefits of dietary supplements could not be not assessed in subjects completing military training exercises due to lack of reliable temporary threshold shift (TTS) (Le Prell et al., 2011), no benefit was observed in a follow-up laboratory-based clinical trial (NCT00808470; Le Prell et al., 2016)

An alternative approach that may prove fruitful in the long run is the use of indices that provide an overall dietary quality metric, given the assumption that nutrients are not acting in isolation. Analysis of the NHANES database indicated a relationship in which better high-frequency thresholds were measured in those with diets that were closer to meeting U.S. recommended dietary allowance (RDA) recommendations ("Good" and "Intermediate" diets in Figure 7.1). For complete details of an original quintile-based analysis, readers are referred to the original report (Spankovich and

Table 7.3 — Otoprotective agents that are being developed for human use. Product names listed here and elsewhere in this chapter do not imply endorsement of any product; product information is provided to illustrate the information available to the public on the internet. Endnotes are used to highlight patents that protect the commercial development rights for each of these agents; intellectual property protection through the patent process is critical to the development of any putative otoprotective agent if there is to be commercialization of a product that patients can then access (Patino, 2009; Le Prell, 2016), but the resulting conflict of interest requires transparent disclosure.[1,2,3,4,5,6]

Agent	Presumed Mechanism	Animal Data	Human Investigation	Current Status
N-acetylcysteine (NAC)	Provides cysteine, used in GSH synthesis Scavenges hydroxyl radicals and hydrogen peroxide	Multiple studies show reduced PTS, but with variable protection across studies (for reviews, see Le Prell & Bao, 2012; Kopke et al., 2007; Le Prell & Lobarinas, 2015; Motalebi Kashani et al., 2013)	Failure to detect TTS in control subjects (Lin et al., 2010; Lindblad et al., 2011; Doosti et al., 2014) No TTS prevention (Toppila et al., 2002; Kramer et al., 2006) TTS prevention reported (Doosti et al., 2014) PTS prevention for subset of metrics (Kopke et al., 2015)	Available over-the-counter as a dietary supplement Approved by the FDA for acetaminophen poisoning
NAC in combination with 4-hydroxy alpha-phenyl-tert-butyl-nitrone (4-OHPBN)	4-OHPBN traps hydroxyl radicals, superoxide anions, and other free radicals (see Floyd et al., 2008)	Reduced PTS (Choi et al., 2008, 2011, 2014a; Ewert et al., 2012; Lu et al., 2014)	None listed on clinical trials.gov as of the writing of this chapter	Not currently approved for human use outside of Investigational New Drug (IND) studies Otologic Pharmaceutics Inc. is developing NHPN-1010: combination of NAC and HPN-07 (https://clinicaltrials.gov/ct2/show/NCT02259595)
D-methionine (D-Met)	Metabolized to methionine, an amino acid that is a precursor to cysteine Effects may be dose-, noise-, and tissue-specific (Fox et al., 2016)	Reduced cisplatin-induced hearing loss (for review, see Campbell & Le Prell, 2012) Reduced aminoglycoside antibiotic-induced hearing loss (for review, see Campbell & Le Prell, 2012; see also new data from Fox et al., 2015; Campbell et al., 2016) Reduced TTS and PTS (for review, see Le Prell & Bao, 2012; see also new data from Claussen et al., 2013; Lo et al., 2013; Rewerska et al., 2013)	NCT01345474	Obtained from protein sources such as meats, dairy products, beans, nuts, and seeds D-methionine not currently approved for human use outside of Investigational New Drug (IND) studies approved by the FDA MRX-1024 developed and used previously by Molecular Therapeutics in completed IND studies (Hamstra et al., 2010) MetArmor is developing a novel D-Met formulation for use in future IND studies Methionine, DL-methionine, and L-methionine are available as dietary supplements
Ebselen	GPx mimic and inducer; speeds redox reactions	Reduced TTS and PTS (for reviews, see Le Prell & Bao, 2012; Azad and Thomas, 2014)	NCT01444846 (Kil et al., 2014)	Not currently approved for human use outside of Investigational New Drug (IND) studies

(Abbreviations: ACEMg, vitamins A, C, E, and magnesium; FDA, Food and Drug Administration; GPx, glutathione peroxidase; GSH, glutathione; NMDA, *N*-methyl-D-aspartate; PTS, permanent threshold shift; SOD, superoxide dismutase; TTS, temporary threshold shift)

Table 7.3 — Otoprotective agents that are being developed for human use (cont.)

Agent	Presumed Mechanism	Animal Data	Human Investigation	Current Status
β-carotene, vitamin A	Antioxidant; increases SOD, catalase, and GSH	Reduced PTS (for review, see Le Prell & Bao, 2012)	Epidemiological analyses mixed (for reviews see Le Prell & Spankovich, 2013; Spankovich & Le Prell, 2013) ACEMg did not prevent TTS (NCT00808470; Le Prell et al., 2016)	Obtained from dietary sources, including beef, liver, and fish; green leafy vegetables; and other green, orange, and yellow vegetables Retinol and retinyl esters obtained from meat; converted to retinol in the small intestine, and stored in liver until needed Available over-the-counter as a dietary supplement
Vitamin C	Antioxidant; increases SOD, catalase, GSH, and GPx	Reduced PTS (for review, see Le Prell & Bao, 2012)	Epidemiological analyses mixed (for reviews see Le Prell & Spankovich, 2013; Spankovich & Le Prell, 2013) ACEMg did not prevent TTS (NCT00808470; Le Prell et al., 2016)	Obtained from dietary sources, including citrus fruits, kiwi, strawberries, cantaloupe; vegetables such as broccoli, red and green peppers Available over-the-counter as a dietary supplement
Vitamin E	Antioxidant	Reduced PTS (for review, see Le Prell & Bao, 2012)	Epidemiological analyses mixed (for reviews see Le Prell & Spankovich, 2013; Spankovich & Le Prell, 2013) ACEMg did not prevent TTS (NCT00808470; Le Prell et al., 2016)	Obtained from dietary sources, including nuts, seeds, and vegetable oils, as well as green leafy vegetables and fortified cereals Available over-the-counter as a dietary supplement
Magnesium	Antioxidant, vasodilator, NMDA antagonist	Reduced PTS (for review, see Le Prell & Bao, 2012)	Prevention of TTS (Attias et al., 2004) and PTS (Joachims et al., 1993; Attias et al., 1994) ACEMg did not prevent TTS (NCT00808470; Le Prell et al., 2016)	Obtained from dietary sources, including green vegetables, some legumes (beans and peas), nuts and seeds, and whole, unrefined grains Available over-the-counter as a dietary supplement
Alpha-lipoic acid	Antioxidant; stimulates GSH synthesis; binds (chelates) free metal ions	Reduced cisplatin-induced hearing loss (Rybak et al., 1999; Rybak & Somani, 1999; Ozkul et al., 2014) Reduced aminoglycoside antibiotic induced hearing loss (Conlon & Smith, 2000; Wang et al., 2012)	Prevention of TTS (Quaranta et al., 2012)	Lipoic acid is a fatty acid produced endogenously in mitochondria; alpha-lipoic acid is a synthetic version of lipoic acid Obtained from red meat, organ meat (such as liver), and yeast Alpha-lipoic acid is sold over the counter as a dietary supplement

[1] **Kopke, R.D., Henderson, D., and Hoffer, M.E. (2003):** Prevention or Reversal of Sensorineural Hearing Loss (SNHL) Through Biologic Mechanisms. Assigned to: The United States of America as represented by the Secretary of the Navy. United States Patent Trademark Office, Number 6,649,621, US. pp. 1-25.

[2] **Kopke, R.D. and Floyd, R.A. (2013):** Methods for Treating Acute Acoustic Trauma. Assigned to: Oklahoma Medical Research Foundation. United States Patent Trademark Office, Number 8,420,595, US. pp. 1-8.

[3] **Campbell, K.C.M. (2001):** Therapeutic Use of D-Methionine to Reduce The Toxicity of Ototoxic Drugs, Noise, and Radiation. Assigned to: Southern Illinois University School of Medicine. United States Patent Trademark Office, Number 6,265,386, US. pp. 1-23.

[4] **Campbell, K.C.M. (2008):** Therapeutic Use of Methionine-Derivatives to Reduce the Toxicity of Noise. Assigned to: Southern Illinois University School of Medicine. United States Patent Trademark Office, Number 7,423,065, US. pp. 1-23.

[5] **Kil, J. and Lynch, E. (2010):** Methods for Treating Hearing Loss. Assigned to: Sound Pharmaceuticals. United States Patent Trademark Office, Number 7,820,640, US. pp. 1-14.

[6] **Miller, J.M., Le Prell, C.G., Schacht, J., and Prieskorn, D. (2011):** Composition and Method of Treating Temporary and Permanent Hearing Loss. Assigned to: The Regents of the University of Michigan. United States Patent Trademark Office, Number 7,951,845 US. pp. 1-13.

Le Prell, 2013). More recent data showed a robust interaction with noise, with the effects of noise exposure appearing to be increased as a function of poorer diet, although the data were retrospective and causality cannot be determined (Spankovich and Le Prell, 2014).

Complex Interactions Between Noise, Ototoxicants, and Other Factors

Interactions between agents or factors that are common to our lives modify risk of developing a hearing loss. These factors include age, sex, race, socioeconomic and lifestyle factors, physical work load, and use of medications (Toppila et al., 2000; Ecob et al., 2008). Additionally, cardiovascular disease, hypertension, and diabetes are known to increase the risk for hearing loss (Agrawal et al., 2009).

Age

Age must be considered when examining hearing disorders, given that "normal" hearing thresholds are higher in older individuals. The assumptions for "normal" age-related change in humans can be drawn from longitudinal data, which typically reveal changes on the order of 0.7 to 1 dB per year, with the rate of change varying with frequency (more rapid change at higher frequencies), age (more rapid change at older ages), and sex (more rapid change in men) (Brant and Fozard, 1990; Ostri and Parving, 1991; Pearson et al., 1995; Morrell et al., 1996; Cruickshanks et al., 2003; Lee et al., 2005; Echt et al., 2010; Kiely et al., 2012). However, it is necessary to remember that although many people experience a decrease in hearing acuity with age, others do not. It is not possible to predict who will and who will not develop hearing loss with aging. Thus, when calculating significant threshold shifts, age-correcting hearing thresholds will overestimate the expected hearing loss for some people and underestimate it for others.

A key reason age has to be taken into account when considering potential effects of noise or chemicals on the inner ear is that young animals are more vulnerable to these insults. Ohlemiller et al. (2000) reported changes in vulnerability between 1–2 months of age and 5–7 months of age for CBA/CaJ, C57BL/6J, and BALB/cJ mice; Kujawa and Liberman (2006) narrowed this window to 8–16 weeks, with 8-week CBA/CaJ mice being more vulnerable than 16-week-old mice. If there is a critical period for gerbils, it is presumably similarly early, as there were no differences when 6- to 8-month-old gerbils were compared to 34- to 38-month-old gerbils (Boettcher, 2002). The increased vulnerability of young animals extends to chemicals in that young rats (14 weeks of age) were more vulnerable to the effects of styrene than aged rats (Campo et al., 2003). Toluene and noise were found to accelerate age-related hearing loss (ARHL) in mice with a genetic predisposition for ARHL, but not in mice from a strain without this predisposition (Li et al., 1992). Even moderate-intensity noise can accelerate the presbycusis process (Campo et al., 2011). Similar but less conclusive results were also reported for styrene exposure. Although these studies clearly suggest that populations exposed to chemical toxicants at young ages may be more susceptible to hearing loss later in life, this has not yet been documented in humans and there are no data establishing a critical age at which vulnerability decreases.

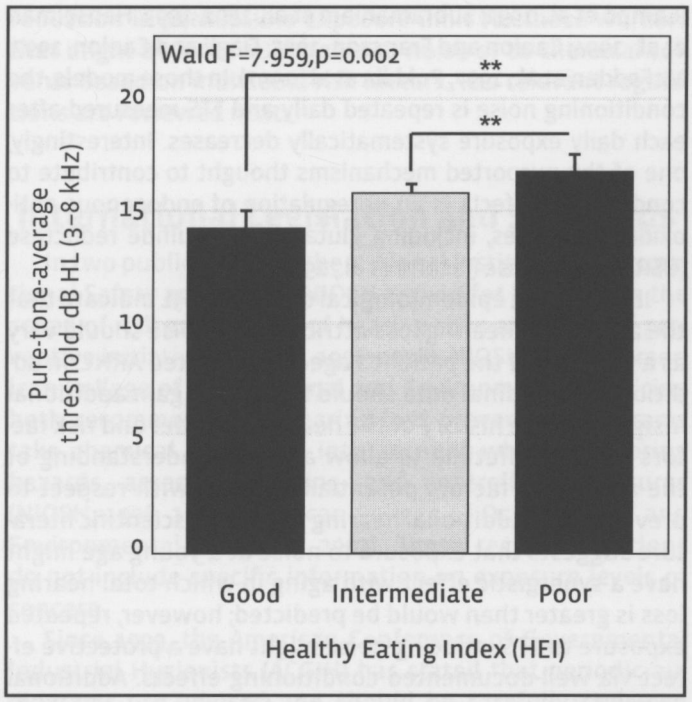

Figure 7.1 — Average pure-tone-average threshold at 3, 4, 6, and 8 kHz was better in those with diets that met U.S. Recommended Dietary Allowance standards. As dietary quality decreased, poorer thresholds were measured.

A second key reason that interactions between age and noise must be considered is that early noise exposure has the potential to influence later ARHL. Noise exposure that results in a TTS can result in an immediate and permanent loss of synaptic ribbons and a decrease in ABR Wave I amplitude, with long-term degeneration of the spiral ganglion and overt hearing loss exceeding expected ARHL later in the lifespan (Kujawa and Liberman, 2006, 2009; Lin et al., 2011; Furman et al., 2013). More recent data replicate these early findings and extend them in showing that lower-level exposures producing a smaller TTS do not result in loss of synaptic ribbons or decrease in ABR amplitude, including conditions with vulnerable young animals and conditions in which animals are followed for extended periods of time (Hickox and Liberman, 2014; Fernandez et al., 2015; Jensen et al., 2015). The data showing a neuropathic effect of TTS-inducing noise exposure contrast with the otoprotective effects attributed to other TTS-inducing noise exposures, in which the ear was reliably "conditioned" or "toughened" through repeated low-intensity noise exposure that rendered ears more resistant to later, louder noise

(Campo et al., 1991; Subramaniam et al., 1992, 1993; Henselman et al., 1994; Canlon and Fransson, 1995; Dagli and Canlon, 1997; McFadden et al., 1997; Pukkila et al., 1997). In those models, the conditioning noise is repeated daily and TTS measured after each daily exposure systematically decreases. Interestingly, one of the purported mechanisms thought to contribute to conditioning effects is an upregulation of endogenous antioxidant enzymes, including glutathione-disulfide reductase (GSR) and catalase (Jacono et al., 1998).

In summary, epidemiological data on ARHL indicate that the amount of hearing loss attributed to noise should vary as a function of the patient's age and expected ARHL. In addition, longitudinal data should be used to gain additional insight into the history of the hearing disorder and risk factors over the lifetime to allow a better understanding of the additional factors potentially at play with respect to prevention of additional hearing loss. Basic scientific literature suggests that exposure to noise at a young age might have a synergistic effect with aging in which total hearing loss is greater than would be predicted; however, repeated exposure to TTS-inducing noise might have a protective effect via well-documented conditioning effects. Additional research is necessary to understand the potential hazards of noise that results in temporary changes in hearing.

Gender and Race

Gender and race seem to be associated with susceptibility to NIHL; however, neither is completely understood. Data from animal studies provide some insight into interactions between gender and noise injury. Whereas a study in gerbils revealed no apparent gender difference in NIHL (Boettcher, 2002), data from noise-exposed chinchillas indicated that female chinchillas were more sensitive to high-frequency NIHL and less sensitive to low-frequency NIHL than males (McFadden et al., 1999). In contrast to these animal studies, human studies examining male and female workers in an automobile stamping plant (Brink et al., 2002), male and female farmers (Beckett et al., 2000; Hwang et al., 2001), and male and female enlisted personnel in the U.S. Navy and Marine Corps (Bohnker et al., 2002) found that men were more likely to suffer NIHL than women were in all of these employee cohorts. The issue of sex and occupational NIHL is confounded in that both environmental and occupational noise exposure histories can be heavily influenced by sex. Multiple datasets suggest early NIHL is observed in males more often than in females (Costa et al., 1988; Holmes et al., 1997; Niskar et al., 2001), although more recent datasets suggest sex differences have been eliminated as young females have "caught up" to males (Henderson et al., 2011; Sekhar et al., 2011).

Data from animal studies perhaps provide some insight into interactions between race/ethnicity and noise injury, in that albino animals show greater noise-induced deficits than pigmented animals (Conlee et al., 1986, 1988), leading to the suggestion that interactions between race and susceptibility to noise could be explained by differences in melanin (Barrenas and Lindgren, 1991; Barrenas, 1997). Caucasian personnel were reported to be more susceptible to the toxic effects of metal-fabricating noise than others (Ishii and Talbott, 1998), and hearing loss in Caucasian Emergency Medical Service firefighters was greater than that of black workers (Jerger et al., 1986). Other studies conducted with groups with similar jobs and exposures have also indicated that Caucasian males have poorer auditory thresholds and higher prevalence of NIHL and African American females have the lowest prevalence of hearing loss (Szanto and Ionescu, 1983; Driscoll and Royster, 1984). Regarding solvents, sex was a significant covariate in a multicenter study on styrene-exposed workers (Morata et al., 2011).

Socioeconomic and Lifestyle Factors

Low social class in childhood and adulthood is associated with poorer hearing thresholds (Ecob et al., 2008) and is likely to interact with occupational risks, leisure noise or nonoccupational chemical exposures, and medical history factors such as middle ear disease, lack of appropriate treatment, or use/abuse of medication.

Studies on the interaction between hearing loss and smoking indicate that heavy smoking can affect hearing (Sharabi et al., 2002; Burr et al., 2005; Wild et al., 2005) and interact with noise, thus causing a more severe hearing loss in humans (Starck et al., 1999; Toppila et al., 2000; Itoh et al., 2001; Mizoue et al., 2003). Other epidemiological investigations of solvents have controlled for smoking, and no significant associations were reported (Morata et al., 1993, 1997, 2002; Sliwinska-Kowalska et al., 2001, 2003).

Interactions between alcohol consumption and NIHL are also of interest. Although alcohol might be consumed in noisy venues (bars, clubs), most of the literature addresses the interaction between hearing and alcohol without consideration of noise. Although two large studies showed no relationship between total alcohol consumption and professionally diagnosed hearing loss in men (Curhan et al., 2011) or self-reported hearing loss in women (Curhan et al., 2015), other studies in which precise threshold information was available reported moderate hearing protection as a function of alcohol intake (Fransen et al., 2008; Gopinath et al., 2010; Dawes et al., 2014). Protection of auditory function by alcoholic beverages could perhaps be explained by their antioxidant properties, which vary across beverages (Gu et al., 1999; Dobiasova et al., 2002; Koga et al., 2007; Magalhaes et al., 2009). In contrast to these long-term protective effects, alcohol consumption resulted in acute threshold shifts during alcohol intoxication (Upile et al., 2007) and potentiated the effect of solvent exposure on hearing, as demonstrated in animals (Campo and Lataye, 2000). Information about alcohol consumption can be considered sensitive and can be difficult to obtain in human studies.

Physical Workload

Several reports document decreased vulnerability to TTS as a function of better physical fitness (Manson et al., 1994; Kolkhorst et al., 1998); in contrast to this positive relationship, simultaneous noise exposure and physical exercise has been shown to increase TTS (Lindgren and Axelsson, 1988). Similarly, studies indicate that the total absorbed styrene dose can be increased six-fold with physical work and increased respiratory rate (Engström et al., 1978). It has been suggested that auditory effects of solvents may be observed at lower concentrations in humans because humans are generally exposed to solvents in combination with a multitude of other factors (several combined exposures, physical demands, etc.), whereas animal experiments typically involve isolated chemical exposures (Lataye et al., 2005).

Medication

Finally, the ototoxicity of therapeutic drugs has been recognized for a long time, and interactions across insults are well known (Boettcher et al., 1987). Despite synergistic ototoxicity, interactions between medication and work-related risk factors have rarely been examined. In addition to interaction between noise and aminoglycoside antibiotics, and noise and cisplatin, the potential for synergistic interactions between noise and over-the-counter medications should be considered. Acetylsalicylic acid is the active agent in aspirin, and high doses of this agent clearly result in threshold shift and/or tinnitus (Brien, 1993; Guitton et al., 2003; Sheppard et al., 2014). A synergistic interaction between acetylsalicylic acid and toluene was shown by Johnson (1992). Acetylsalicylic acid did not cause hearing loss but instead potentiated the ototoxic effect caused by toluene. In contrast to the potentiation of the chemical exposure, aspirin, has prevented NIHL as well as hearing loss induced by aminoglycoside antibiotics (Sha et al., 2006). Epidemiological data are clearly of interest; negative effects of aspirin on hearing were reported for males, but no relationship was observed in females (Curhan et al., 2010, 2012). Acetaminophen was associated with hearing loss in both males and females (Curhan et al., 2010, 2012). Finally, ibuprofen was associated with hearing loss in females (Curhan et al., 2012), and non-steroidal anti-inflammatory drug (NSAID) use (queried separately from aspirin and acetaminophen, although we note here that the category of NSAIDs includes aspirin, ibuprofen, and naproxen in addition to a variety of other active agents) was associated with hearing loss in males (Curhan et al., 2010). Interactions between these other pain medications and noise or chemicals are of interest since these drugs are also likely to be used by workers exposed to noise and chemicals, but data addressing potential interactions are not yet available.

Given the paucity of data, current regulations do not provide any guidance on individual risk factors. There is no reduction in permissible exposure limit for those workers that might be more vulnerable to noise or to chemical solvents based on individual risk factors. The relevant regulations are reviewed next.

International Legislation and Standards

In two publications by the National Institute for Occupational Safety and Health, NIOSH argued for broadening the scope of risk assessment of hearing risks at work and preventive initiatives (NIOSH, 1996, 1998). NIOSH and the American College of Occupational and Environmental Medicine both recommend that hearing loss prevention programs take chemical exposures into account when monitoring hazards, assessing hearing, and controlling exposures (NIOSH, 1996, 1998; American College of Occupational and Environmental Medicine, 2003). These recommendations do not include specific information on exposure levels of concern.

Since 1999, the American Conference of Governmental Industrial Hygienists (ACGIH) has stated that periodic audiograms are advised and should be carefully reviewed in settings where there may be exposures to noise and to carbon monoxide, lead, manganese, styrene, toluene, or xylene. Other substances under investigation for ototoxic effects include arsenic, carbon disulphide, mercury and trichloroethylene (American Conference of Governmental Industrial Hygienists, 2009). The U.S. Army started requiring consideration of ototoxicant exposures for inclusion in hearing conservation programs in 1998, "particularly when in combination with marginal noise" (U.S. Department of the Army, 1998); in 2003, they offered the most detailed and specific recommendation to date, stating that since the exposure threshold for ototoxic effects is not known, audiometric monitoring is necessary to find out if the substance is affecting the hearing of exposed workers (U.S. Army Center for Health Promotion and Preventive Medicine, 2003). Yearly audiograms are recommended for workers whose airborne exposures (without regard to the use of respiratory protection) are at 50% of the most stringent criteria for occupational exposure limits (OELs) (either of the U.S. OSHA permissible exposure limit or the ACGIH threshold limit value) for toluene, xylene, *n*-hexane, organic tin, carbon disulphide, mercury, organic lead, hydrogen cyanide, diesel fuel, kerosene fuel, jet fuel, JP-8 fuel, organophosphate pesticides, or chemical warfare nerve agents, regardless of the noise level (U.S. Army Center for Health Promotion and Preventive Medicine, 2003).

Best practice guidelines recommending hearing tests for those exposed to ototoxic agents were also published in Australia and New Zealand, without information on exposure levels (AS/NZS 1269, 2005). Legislation regarding compensation for hearing loss associated with chemical exposure at work has changed in Australia (WorkCover, 2002) and Brazil (Ministério da Previdência e Assistência,

1999), making it possible for workers to apply for compensation for hearing loss because of exposure to ototoxicants in the workplace.

In February 2003, the European Parliament published the Directive 2003/10/EC on minimum health and safety requirements regarding the exposure of workers to the risks arising from noise. In the Directive, it states that when carrying out risk assessments, employers should "...give particular attention to: any effects on workers' health and safety resulting from interactions between noise and work-related ototoxic substances..." (European Parliament and the Council of the European Union, 2003). Some European countries have reduced their exposure limits to styrene due to their ototoxic potential (Hansen et al., 2002; Ministre du Travail de l'emploi et de la santé, 2012). In April 2004, because of its demonstrated ototoxicity, toluene was labeled as R48/20: "Danger of serious damage to health by prolonged exposure through inhalation." Toluene-induced chronic impairment of auditory function had been demonstrated in a number of animal studies and substantiated by morphological evidence of cell loss in the rat cochlea, with existing data suggesting that humans are sensitive to this effect at exposure levels that may be encountered in the working environment (Hansen et al., 2002; European Commission, 2004).

Besides the present chapter, comprehensive evaluations of ototoxicants (Vyskocil et al., 2009) and of the hazards of combined workplace exposure to noise and ototoxicants (European Agency for Safety and Health at Work, 2009) have been published by other bodies. The Canadian Occupational Health and Safety Research Institute (Vyskocil et al., 2009) did not include data on the interaction between noise and chemicals. Still, the conclusions agree with those of the present document in classifying lead and its inorganic compounds, toluene, styrene and trichloroethylene, as "ototoxic substances."

The report published by the European Agency for Safety and Health (European Agency for Safety and Health at Work, 2009) included noise interactions and focused on the qualitative properties of chemicals inducing ototoxic effects. The report from the European Agency also highlights policies from specific member states and the possible impact of the 2007 regulations, Registration, Evaluation, Authorisation and Restriction of Chemical substances (REACH), which will not be repeated here.

The 2010 Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals on Occupational Exposure to Chemicals and Hearing Impairment discussed the Hoet and Lison (2008) proposal of a "noise notation" inspired by the widely used "skin notation" (Johnson and Morata, 2010). The proposed notation could be added to the OELs of chemical agents for which there is significant concern about a possible ototoxic effect, e.g., when experimental data suggest that ototoxicity is the critical health effect or that ototoxic effects occur at a level close to the OEL. As combined exposure (e.g., chemical and noise) is currently not taken care of in the regular OEL setting procedure, a noise notation can be used to indicate an increased risk of hearing loss after exposure to the chemical with concurrent noise exposure. Since its proposal, the noise notation has been adopted in France, Switzerland, and Sweden.

In 2018, the American Conference of Governmental Industrial Hygienists (ACGIH) put forward a similar proposal in its publication on Threshold Limit Values and Biological Exposure Indices (American Conference of Governmental Industrial Hygienists, 2018). A note in the Noise Section (page 74) states: "The designation OTO for hearing disorders in the 'Notations' column highlights the potential for a chemical to cause hearing impairment alone or in combination with noise, even below 85 dBA. The OTO notation is reserved for chemicals that have been shown, through animal studies or human experience, to adversely affect auditory capacity, usually manifested as a permanent audiometric threshold shift (difficulty in detecting sounds) as well as difficulties in processing sounds. Certain solvents, predominantly aromatic hydrocarbons, but also some halogenated solvents, metals and chemicals that cause anoxia, have been shown to cause hearing disorders. Some solvents appear to act synergistically with noise, whereas carbon monoxide potentiates noise effects. The OTO notation is intended to focus attention, not only on engineering controls, administrative controls and personal protective equipment needed to reduce airborne concentrations, but also on other means of preventing excessive combined exposures with noise to prevent hearing disorders. Specifically, affected employees may need to be enrolled in hearing conservation and medical surveillance programs to more closely monitor auditory capacity."

Finally, a new informational bulletin developed by OSHA and NIOSH (2018) raises awareness of this issue, provides examples of ototoxic chemicals, lists the industries and occupations at risk, and provides prevention information (https://www.cdc.gov/niosh/docs/2018-124/pdfs/2018-124.pdf?id=10.26616/NIOSHPUB2018124).

Simple Solutions for a Complex Problem?

Considering that environmental and occupational factors other than noise can affect hearing, one needs to rethink steps that can be taken to prevent hearing disorders. Traditional hearing conservation practices do not take into account the potential risk to hearing posed by chemical exposures in the workplace. The strongest argument for revising hearing loss prevention programs is still, unfortunately, the ongoing high occurrence of work-related hearing loss in industrialized countries.

Preventive strategies can be applied at any stage along the natural history of disease or injury, or in this case hearing loss, with the goal of preventing further deterioration. Primary prevention seeks to prevent onset of disease or injury and generally targets specific causes and

risk factors. For example, workers with normal hearing and minimal noise exposure history should be provided training and hearing protection devices prior to starting a new position. Secondary prevention seeks to detect and treat preclinical pathology and control disease or injury progression. Screening procedures (such as yearly hearing tests) are an example. Once a disease or injury has developed, tertiary prevention seeks to soften the impact on the patient's function, longevity, and quality of life. In terms of hearing loss, this can include increased conservation strategies and rehabilitation efforts, such as hearing aids and assistive listening devices (Smith, 1998; Le Prell and Spankovich, 2013). These stages of prevention are not independent, and often comparable strategies can be applied at each stage. However, the lack of effect at one stage may call into question the viability of that strategy at the next stage.

Strategies to control or prevent injury fall on a spectrum, where active and passive measures are at opposite poles defined by the amount of behavioral response required by the individual. At one extreme are "passive" measures, which do not require the cooperation of the individual. Examples of a passive measure include "quiet equipment" (or removal of the noise source) and eliminating ototoxicants in lieu of nontoxic alternatives. Passive strategies have historically been most effective for prevention of disease and injury, as no specific action is required by the individual (Haddon, 1980). At the other extreme are active measures that require the individual to make a behavioral change. The most common example regarding occupational health would be appropriate use of personal protection. Both passive and active strategies have important roles in the control of disease and injury. The application of passive, active, or mixed approaches to prevention of hearing loss is influenced by cost, benefit, effectiveness, and role of individual responsibility and individual cooperation.

Human behavior is not readily changed. The Hearing Conservation Amendment was promulgated in 1983 (OSHA, 1983). However, the use of HPD among industry and military populations remains low, despite training and worker knowledge of the consequences (Tak et al., 2009). The explanations for this likely include attitude toward noise, acceptance of noise as "part of job," incomplete or inadequate training, low perceived susceptibility and severity of hearing loss, prior experience of hearing loss or tinnitus, idea that hearing aids or other intervention will return normal hearing, poor enforcement of safety rules, peer influence, comfort and fit of HPD, diminished communication, localization, and situational awareness (Daniell et al., 2006; Casali et al., 2009; Davies et al., 2009, 2012; Reddy et al., 2012). To improve the effectiveness of hearing conservation programs, use of health behavior theory may be of benefit. Health behavior theory can be classified into three primary types: intrapersonal theories, an individual's characteristics that influence behavior; interpersonal theories, influence of external factors such as peers and social identity; and organizational and community theory, influence of rules, regulations, and policy. An excellent review of health behavior theories is available to the interested reader (National Cancer Institute, 2005).

The evidence on the effectiveness of current interventions to reduce the prevalence of and risks for work-related hearing loss (Tikka et al., 2017) indicate there is a need to rethink the approaches commonly used. In the realm of this chapter, some components of a hearing conservation program that are likely to increase effectiveness of such interventions include:

1. The initial steps of hearing loss prevention programs are hazard assessment (of all hazardous agents) and control. **The most effective way to prevent hearing disorders from noise or chemical exposure is to remove the source of hazardous exposures from the workplace, for example, by engineering controls, using personal protective equipment, or finding alternatives to minimize exposure, such as reducing the duration of exposure (passive strategies).** Whenever hazardous noise or chemicals exist in the workplace, measures to reduce exposure levels to protect exposed workers and to monitor the effectiveness of these intervention processes are required by law. Some suggested sources of information include Suter (2009), NIOSH (1998), and the Encyclopaedia of Occupational Health and Safety (International Labour Organization, 2012).
2. The next step is to re-examine the *eligibility criteria for inclusion in hearing loss prevention programs.* **Preventive strategies that are used to protect workers from noise exposure will not necessarily protect workers from chemical exposure or the interaction between agents.** When evidence that chemicals in the workplace can affect hearing is considered, then hearing loss prevention initiatives may be needed even in workplaces where noise exposure does not exceed 85 dBA.
    a. As described above, the U.S. Army offers recommendations for revising hearing loss prevention program eligibility criteria with chemical exposure.
    b. The Nordic Expert Group criteria document (Johnson and Morata, 2010) also provides information on ototoxic chemicals investigated to date.
3. The third step is deciding what industrial hygienists, safety professionals or audiologists should do *when the ototoxicity of a chemical present in the workplace has not been tested.* **How can professionals decide if there should be a concern about auditory effects for chemical exposures that have not been tested for ototoxicity?** One approach was proposed at the 2002 *Best Practices Workshop:*

Combined Effects of Chemicals and Noise on Hearing (Morata, 2003). The consensus recommendation was to gather information on the agent's general toxicity, nephrotoxicity, and neurotoxicity (since most of the chemicals that affect the auditory system are potentially neurotoxic and/or nephrotoxic) along with complaints from exposed populations. Information on whether a chemical produces free radicals could help determine whether a chemical should be screened for potential ototoxicity. In summary, when hazard information on a specific agent or combination of agents or exposures is not available, one should seek information on the toxicity of individual agents present (e.g., common target organs) or exposure combinations.

4. **Audiological monitoring or referral should be implemented if ototoxicity, nephrotoxicity, or neurotoxicity are reported, or if the agent induces oxidative stress.** Hearing loss from ototoxicity is typically bilaterally symmetrical and irreversible. Similar to the effect of noise exposure, a high-frequency "notch" on the audiogram is often present following long-term exposure to ototoxic chemicals, although a wider range of frequencies may be affected (i.e., from 2000 to 8000 Hz; see Morata, 2003; Sliwinska-Kowalska, 2007).
5. **Audiological monitoring should not be limited to pure-tone threshold metrics.** The effects of environmental and/or occupational chemicals are not restricted to the cochlea. Reports have indicated that retrocochlear and central effects can also be linked to these exposures. Pure-tone threshold tests do not identify the cause of hearing loss and may not fully reveal hearing difficulties. Sound may be detected (i.e., loud enough to be heard), but it might lack clarity and thus speech recognition may be compromised, particularly in background noise. Pure-tone audiometry provides information on detection thresholds but not on the perceptual quality and discrimination. Use of a questionnaire assessing difficulty with speech recognition or other auditory problems beyond threshold loss may help reveal additional effects of the chemical or noise on the auditory system. Professionals should take note if workers complain of hearing difficulties not explained by the audiometric results and consider referring the worker to an audiologist for a complete audiological evaluation.
6. **Risk should be assessed through an interview or questionnaire that establishes exposure history for both noise and chemicals as another important element in the diagnosis of hearing loss from noise or chemicals.** Survey instruments should include medical and nonmedical risk factors associated with the condition and exposure to other risk factors. Other important questions are use of hearing aids, ototoxic medication, and the experience of "ringing" in the ears (tinnitus) as well as hypersensitivity to sound (hyperacusis).
7. **Personal protective equipment should be advocated.** Despite the challenges associated with the effective use of personal protective equipment, personal protective devices (hearing protection devices and respirators) are often adopted in lieu of controlling hazardous exposures (active strategy). For information on personal protective equipment to control for chemical exposures, see (http://www.cdc.gov/niosh/topics/chemical.html).

Summary

Noise is a universally recognized risk factor for hearing loss, and the occupational health community is well aware of the preventive and rehabilitative needs associated with it. However, certain non-acoustic factors in the workplace may directly affect hearing, or interact with noise, and are therefore considered to be possible contributors to individual variability in susceptibility to noise-induced hearing loss. Metals, asphyxiants, pesticides, and organic solvents fall within this category. The adverse auditory effects of chemical toxicants have been systematically investigated during the past two decades, both in animal studies in the laboratory and in human field and clinical studies. Some chemicals not only affect the sensory organ of the auditory system, but also adversely affect central auditory structures. Noise is also increasingly considered to not only affect the organ of Corti, but also adversely affect central auditory structures. Both noise and chemicals, such as solvents, result in adverse auditory effects due to a combination of oto- and neurotoxicity. Ototoxicity induces outer hair cell dysfunction in the cochlea, whereas neurotoxicity induces central auditory dysfunction. The main audiological sign of ototoxicity is poorer hearing thresholds than expected, relative to age. Outer hair cell loss can also be detected using otoacoustic emission tests. Audiological signs of neurotoxicity may or may not include poorer hearing thresholds, in addition to difficulties discriminating sounds such as speech, particularly in adverse listening conditions. Evidence of chemical-induced hearing loss has prompted the proposal of new guidelines and standards for hearing loss prevention.

In broadening our thinking about interventions to prevent hearing loss, we should become familiar with the evidence on otoprotection as well as principles of health promotion. To date, robust protection has been demonstrated only in animal subjects. Although, as of the writing of this chapter, there are no FDA-approved therapeutics for prevention of NIHL and/or protection of the inner ear, there are multiple clinical trials that have been completed and additional clinical trials are in progress for several different investigational agents (for review, see Le Prell and

Lobarinas, 2015). Because any list provided here would be quickly outdated, interested readers are pointed to the National Institutes of Health Online Clinical Trials Registry (http://clinicaltrials.gov/) for up-to-date information. With confirmation of protection of the human inner ear and approval of label claims by the FDA, there may one day be agents available for protecting the ear against NIHL that occurs despite use of HPDs or when HPDs are not an option. *Although some of the active agents of interest are available in the form of dietary supplements, audiologists and others involved in hearing conservation education should stress to patients and other clients that there are no FDA-approved products for the protection of human hearing.* With respect to dietary supplements marketed in the absence of demonstrated clinical benefit, the authors of this chapter do not advocate specific supplements. Instead, we advocate dietary nutrient intake that meets the U.S. Institute of Medicine RDA (Institute of Medicine, 2004a, 2004b) but does not exceed U.S. Institute of Medicine Tolerable Upper Intake Levels (UL) (Institute of Medicine, 2004c, 2004d). We advocate that recommended nutrient intake be achieved via healthy diets rather than supplements whenever possible for several key reasons. First, it is unlikely that supplements can "replace" a healthy diet given the variety of different vitamins, minerals, and macronutrients that need to come from dietary sources. Second, choosing foods that are high in sugar, fats, or filler is not healthy, even with a dietary supplement. There are data that indicate high-fat and/or high-cholesterol diets may have negative consequences for hearing function. Third, nutrients derived from food sources contain the full spectrum of nutrients and phytochemicals associated with that specific food, whereas supplements do not. For example, Vitamin E has eight iso-forms, but most daily multivitamins include only one of these forms: alpha-tocopherol. Fourth, there are implications for how food is digested and metabolized compared to a capsule, with nutrients that are consumed with food potentially having better bioavailability.

KEY CONCEPTS: Several determinants of health (age, diet, fitness, chronic diseases and related medications, smoking and drinking habits) and exposures outside the workplace can impact hearing. Achieving the goal of hearing loss prevention requires taking some of the factors into consideration. Evidence shows that several chemicals commonly found in the workplace can damage hearing. These chemicals include solvents, paint thinners, degreasers, fuels, exhausts, metals, and pesticides. In addition, some of these toxicants interact with noise in exacerbating hearing loss. Monitoring strategies must include assessment of all hazardous agents (not restricted to noise) and control of exposures; inclusion of workers exposed to ototoxic chemicals in hearing loss prevention programs; and careful analysis of audiometric results and referral of cases of hearing loss that do not seem to be exclusively related to the noise exposure.

Some of the mechanisms of lesion are common for noise and chemicals. They involve reactive oxygen species, also called free radicals. Some of the research confirming these findings has used antioxidants to reduce noise-induced hearing loss. Factors that protect our hearing against noise insult also reduce or prevent hearing loss after ototoxic drugs. Data are limited with respect to attenuation of chemical ototoxicity and neurotoxicity, but protection against chemical ototoxicity appears to be feasible.

In light of this evidence, otoprotective drugs that reduce oxidative stress may provide a novel approach to more effectively prevent hearing loss in the workplace; however, human data are needed. Health promotion programs and information dissemination on hearing loss prevention could have an impact on hearing status. In addition, growing evidence suggests that certain medications/nutrition supplements can facilitate otorescue and promote otoprotection. Nutrient intake that meets the U.S. Institute of Medicine RDA (Institute of Medicine, 2004a, 2004b) but does not exceed U.S. Institute of Medicine Tolerable Upper Intake Levels (UL) (Institute of Medicine, 2004c, 2004d) merits consideration.

References

Abbate, C., Giorgianni, C., Munao, F., and Brecciaroli, R. (1993). "Neurotoxicity Induced by Exposure to Toluene: An Electrophysiologic Study," *Int. Arch. Occup. Environ. Health 64*, 389–392.

Abi-Hachem, R.N., Zine, A., and Van De Water, R.T. (2010). "The Injured Cochlea as a Target for Inflammatory Processes, Initiation of Cell Death Pathways and Application of Related Otoprotective Strategies," *Recent Patents on CNS Drug Discovery 5*, 147–163. doi: 10.2174/157488910791213121.

Agrawal, Y., Platz, E.A., and Niparko, J.K. (2009). "Risk Factors for Hearing Loss in U.S. Adults: Data from the National Health and Nutrition Examination Survey, 1999 to 2002," *Otol. Neurotol. 30*, 139–145. doi: 10.1097/mao.0b013e318192483c.

American Academy of Audiology (2009). Position Statement and Clinical Practice Guidelines: Ototoxicity Monitoring. https://www.audiology.org/wp-content/uploads/2021/05/OtoMonGuidelines.pdf_539974c40999c1.58842217.pdf

American College of Occupational and Environmental Medicine (2003). "ACOEM Evidence-Based Statement: Noise-Induced Hearing Loss," *J. Occup. Environ. Med. 45*, 579–581. doi: 10.1097/00043764-200306000-00001.

American Conference of Governmental Industrial Hygienists (2009). *Documentation of the Threshold Limit Values and Biological Exposure Indices*, American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

American Conference of Governmental Industrial Hygienists (2018). *TLVs® and BEIs®:* Notice of Intended Change, American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

Arnos, K.S. (2008). "Ethical and Social Implications of Genetic Testing for Communication Disorders," *J. Commun. Disord. 41*, 444–457. doi: 10.1016/j.jcomdis.2008.03.001.

AS/NZS 1269 (2005). Occupational Noise Management, 2nd edition, Canberra, Australia.

Attias, J., Weisz, G., Almog, S., Shahar, A., Wiener, M., Joachims, Z., Netzer, A., Ising, H., Rebentisch, H., and Guenther, T. (1994). "Oral Magnesium Intake Reduces Permanent Hearing Loss Induced by Noise Exposure," *Am. J. Otolaryngol. 15*, 26–32. doi: 10.1016/0196-0709(94)90036-1.

Attias, J., Sapir, S., Bresloff, I., Reshef-Haran, I., and Ising, H. (2004). "Reduction in Noise-Induced Temporary Threshold Shift in Humans Following Oral Magnesium Intake," *Clin. Otolaryngol. 29*, 635–641. doi: 10.1111/j.1365-2273.2004.00866.x.

Azad, G.K. and Tomar, R.S. (2014). "Ebselen, A Promising Antioxidant Drug: Mechanisms of Action and Targets of Biological Pathways," *Mol. Biol. Rep. 41*, 4865–4879. doi: 10.1007/s11033-014-3417-x.

Barregård, L. and Axelsson, A. (1984). "Is There an Ototraumatic Interaction between Noise and Solvents?" *Scand. Audiol. 13*, 151–155. doi: 10.3109/01050398409043054.

Barrenas, M.L. and Lindgren, F. (1991). "The Influence of Eye Colour on Susceptibility to TTS in Humans," *Br. J. Audiol. 25*, 303–307. doi: 10.3109/03005369109076602.

Barrenas, M.L. (1997). "Hair Cell Loss from Acoustic Trauma in Chloroquine-Treated Red, Black and Albino Guinea Pigs," *Audiology 36*,187–201. doi: 10.3109/00206099709071973.

Basch, E.M., Servoss, J.C., and Tedrow, U.B. (2005). "Safety Assurances for Dietary Supplements Policy Issues and New Research Paradigms," *J. Herb. Pharmacother. 5*, 3–15. doi: 10.1080/j157v05n01_02.

Beckett, W.S., Chamberlain, D., Hallman, E., May, J., Hwang, S.A., Gomez, M., Eberly, S., Cox, C., and Stark, A. (2000). "Hearing Conservation for Farmers: Source Apportionment of Occupational and Environmental Factors Contributing to Hearing Loss," *J. Occup. Environ. Med. 42*, 806–813. doi: 10.1097/00043764-200008000-00008.

Beskow, L.M., Namey E.E., Cadigan, R.J., Brazg, T., Crouch, J., Henderson, G.E., Michie, M., Nelson, D.K., Tabor, H.K., and Wilfond, B.S. (2011). "Research Participants' Perspectives on Genotype-Driven Research Recruitment," *J. Empir. Res. Hum. Res. Ethics 6*, 3–20. doi: 10.1525/jer.2011.6.4.3.

Boettcher, F.A. (2002). "Susceptibility to Acoustic Trauma in Young and Aged Gerbils," *J. Acoust. Soc. Am. 112*, 2948–2955. doi: 10.1121/1.1513364.

Boettcher, F.A., Henderson, D., Gratton, M.A., Danielson, R.W., and Byrne, C.D. (1987). "Synergistic Interactions of Noise and Other Ototraumatic Agents," *Ear Hear. 8*, 192–212. doi: 10.1097/00003446-198708000-00003.

Bohnker, B.K., Page, J.C., Rovig, G., Betts, L.S., Muller, J.G., and Sack, D.M. (2002). "U.S. Navy and Marine Corps Hearing Conservation Program, 1995–1999: Mean Hearing Thresholds for Enlisted Personnel by Gender and Age Groups," *Mil. Med. 167*, 132–135.

Boullata, J.I. and Hudson, L.M. (2012). "Drug-Nutrient Interactions: A Broad View with Implications for Practice," *J. Acad. Nutrition and Dietetics 112*, 506–517. doi: 10.1016/j.jada.2011.09.002.

Brandt-Lassen, R., Lund, S.P., and Jepsen, G.B. (2000). "Rats Exposed to Toluene and Noise May Develop Loss of Auditory Sensitivity Due to Synergistic Interaction," *Noise Health 3*, 33–44. PMID: 12689441.

Brant, L.J. and Fozard, J.L. (1990). "Age Changes in Pure-Tone Hearing Thresholds in a Longitudinal Study of Normal Human Aging," *J. Acoust. Soc. Am. 88*, 813–820. doi: 10.1121/1.399731.

Brien, J.A. (1993). "Ototoxicity Associated with Salicylates: A Brief Review," *Drug Safe. 9*, 143–148. doi: 10.2165/00002018-199309020-00006.

Brink, L.L., Talbott, E.O., Burks, J.A., and Palmer, C.V. (2002). "Changes Over Time in Audiometric Thresholds in a Group of Automobile Stamping and Assembly Workers with a Hearing Conservation Program," *J. Occup. Env. Hyg. 63*, 482–487. doi: 10.1080/15428110208984737.

Burr, H., Lund, S.P., Sperling, B.B., Kristensen, T.S., and Poulsen, O.M. (2005). "Smoking and Height as Risk Factors for Prevalence and 5-Year Incidence of Hearing Loss: A Questionnaire-Based Follow-Up Study of Employees in Denmark Aged 18–59 Years Exposed and Unexposed to Noise," *Int. J. Audiol. 44*, 531–539. doi: 10.1080/14992020500190045.

Cadigan, R.J., Easter, M.M., Dobson, A.W., Davis, A.M., Rothschild, B.B., Zimmer, C., Sterling, R., and Henderson, G. (2011). "That's a Good Question: University Researchers' Views on Ownership and Retention of Human Genetic Specimens," *Genet. Med. 13*:569–575. doi: 10.1097/gim.0b013e318211a9c2.

Campbell, K.C. (2003). "Ototoxicity: Understanding Oxidative Mechansims," *J. Am. Acad. Audiol. 14*, 121–123. doi: 10.3766/jaaa.14.3.2.

Campbell, K.C.M. and Le Prell, C.G. (2012). "Potential Therapeutic Agents," *Semin. Hearing 33*, 97–113.

Campbell, K.C., Martin, S.M., Meech, R.P., Hargrove, T.L., Verhulst, S.J., and Fox, D.J. (2016). "D-Methionine (D-Met) Significantly Reduces Kanamycin-Induced Ototoxicity in Pigmented Guinea Pigs," *Int. J. Audiol. 55(5)*, 273–278. doi: 10.3109/14992027.2016.1143980.

Campo, P. and Lataye, R. (2000). "Noise and Solvent, Alcohol and Solvent: Two Dangerous Interactions on Auditory Function," *Noise Health 3*, 49–57. PMID: 12689443.

Campo, P., Subramaniam, M., and Henderson, D. (1991). "The Effect of 'Conditioning' Exposures on Hearing Loss from Traumatic Exposure," *Hear. Res. 55,* 195–200. doi: 10.1016/0378-5955(91)90104-h.

Campo, P., Lataye, R., Cossec, B., and Placidi, V. (1997). "Toluene-Induced Hearing Loss: A Mid-Frequency Location of the Cochlear Lesions," *Neurotoxicol. Teratol. 19,* 129–140. doi: 10.1016/s0892-0362(96)00214-0.

Campo, P., Loquet, G., Blachere, V., and Roure, M. (1999). "Toluene and Styrene Intoxication Route in the Rat Cochlea," *Neurotoxicol. Teratol. 21,* 427–434. doi: 10.1016/s0892-0362(99)00010-0.

Campo, P., Lataye, R., Loquet, G., and Bonnet, P. (2001). "Styrene-Induced Hearing Loss: A Membrane Insult," *Hear. Res. 154,* 170–180. doi: 10.1016/s0378-5955(01)00218-0.

Campo, P., Pouyatos, B., Lataye, R., and Morel, G. (2003). "Is the Aged Rat Ear More Susceptible to Noise or Styrene Damage Than the Young Ear?" *Noise Health 5,* 1–18. PMID: 12804208.

Campo, P., Maguin, K., and Lataye, R. (2007). "Effects of Aromatic Solvents on Acoustic Reflexes Mediated by Central Auditory Pathways," *Toxicol. Sci. 99,* 582–590. doi: 10.1093/toxsci/kfm180.

Campo, P., Venet, T., Rumeau, C., Thomas, A., Rieger, B., Cour, C., Cosnier, F., and Parietti-Winkler, C. (2011). "Impact of Noise or Styrene Exposure on the Kinetics of Presbycusis," *Hear. Res. 280,* 122–132. doi: 10.1016/j.heares.2011.04.016.

Campo, P., Venet, T., Thomas, A., Cour, C., Brochard, C., and Cosnier, F. (2014). "Neuropharmacological and Cochleotoxic Effects of Styrene: Consequences on Noise Exposures," *Neurotoxicol. Teratol. 44,* 113–120. doi: 10.1016/j.ntt.2014.05.009.

Canlon, B. and Fransson, A. (1995). "Morphological and Functional Preservation of the Outer Hair Cells from Noise Trauma by Sound Conditioning," *Hear. Res. 84,* 112–124. doi:10.1016/0378-5955(95)00020-5.

Cappaert, N.L., Klis, S.F., Muijser, H., de Groot, J.C., Kulig, B.M., and Smoorenburg, G.F. (1999). "The Ototoxic Effects of Ethyl Benzene in Rats," *Hear. Res. 137,* 91–102. doi: 10.1016/s0378-5955(99)00141-0.

Cappaert, N.L., Klis, S.F., Baretta, A.B., Muijser, H., and Smoorenburg, G.F. (2000). "Ethyl Benzene-Induced Ototoxicity in Rats: A Dose-Dependent Mid-Frequency Hearing Loss," *J. Assoc. Res. Otolaryngol. 1,* 292–299. PMID: 11547809.

Casali, J.G., Ahroon, W.A., and Lancaster, J.A. (2009). "A Field Investigation of Hearing Protection and Hearing Enhancement in One Device: For Soldiers Whose Ears and Lives Depend Upon It," *Noise Health 11,* 69–90. doi: 10.4103/1463-1741.48564.

Chang, S.J., Chen, C.J., Lien, C.H., and Sung, F.C. (2006). "Hearing Loss in Workers Exposed to Toluene and Noise," *Environ. Health. Perspect. 114,* 1283–1286. doi: 10.1289/ehp.8959.

Chen, G.D. and Henderson, D. (2009). "Cochlear Injuries Induced by the Combined Exposure to Noise and Styrene," *Hear. Res. 254,* 25–33. doi: 10.1016/j.heares.2009.04.005.

Chen, G.D., McWilliams, M.L., and Fechter, L.D. (1999). "Intermittent Noise-Induced Hearing Loss and the Influence of Carbon Monoxide," *Hear. Res. 138,* 181–191. doi: 10.1016/s0378-5955(99)00157-4.

Choi, C.H., Chen, K., Vasquez-Weldon, A., Jackson, R.L., Floyd, R.A., and Kopke, R.D. (2008). "Effectiveness of 4-Hydroxy Phenyl N-Tert-Butylnitrone (4-OHPBN) Alone and in Combination with Other Antioxidant Drugs in the Treatment of Acute Acoustic Trauma in Chinchilla," *Free Radic. Biol. Med. 44,* 1772–1784. doi: 10.1016/j.freeradbiomed.2008.02.005.

Choi, C.H., Chen, K., Du, X., Floyd, R.A., and Kopke, R.D. (2011). "Effects of Delayed and Extended Antioxidant Treatment on Acute Acoustic Trauma," *Free Radic. Res. 45,* 1162–1172. doi:10.3109/10715762.2011.605360.

Choi, C.H., Du, X., Floyd, R.A., and Kopke, R.D. (2014a). "Therapeutic Effects of Orally Administrated Antioxidant Drugs on Acute Noise-Induced Hearing Loss," *Free Radic. Res. 48,* 264–272. doi: 10.3109/10715762.2013.861599.

Choi, Y.-H., Miller, J.M., Tucker, K.L., Hu, H., and Park, S.K. (2014b). "Antioxidant Vitamins and Magnesium and the Risk of Hearing Loss in the U.S. General Population," *Am. J. Clin. Nutr. 99,* 148–155. doi: 10.3945/ajcn.113.068437.

Christenhusz, G.M., Devriendt, K., and Dierickx, K. (2012). "To Tell or Not To Tell? A Systematic Review of Ethical Reflections on Incidental Findings Arising in Genetics Contexts," *Eur. J. Hum. Genet. 21(3),* 248–255. doi:10.1038/ejhg.2012.130.

Claussen, A.D., Fox, D.J., Yu, X.C., Meech, R.P., Verhulst, S.J., Hargrove, T.L., and Campbell, K.C. (2013). "D-Methionine Pre-Loading Reduces Both Noise-Induced Permanent Threshold Shift and Outer Hair Cell Loss in the Chinchilla," *Int. J. Audiol. 52,* 801–807. doi: 10.3109/14992027.2013.840933.

Conlee, J.W., Abdul-Baqi, K.J., McCandless, G.A., and Creel, D.J. (1986). "Differential Susceptibility to Noise-Induced Permanent Threshold Shift between Albino and Pigmented Guinea Pigs," *Hear. Res. 23,* 81–91. doi: 10.1016/0378-5955(86)90177-2.

Conlee, J.W., Abdul-Baqi, K.J., McCandless, G.A., and Creel, D.J. (1988). "Effects of Aging on Normal Hearing Loss and Noise-Induced Threshold Shift in Albino and Pigmented Guinea Pigs," *Acta Otolaryngol. (Stockh). 106,* 64–70. doi: 10.3109/00016488809107372.

Conlon, B.J. and Smith, D.W. (2000). "Topical Aminoglycoside Ototoxicity: Attempting to Protect the Cochlea," *Acta Otolaryngol. 120,* 596–599. doi: 10.1080/000164800750000397.

Consumer Reports (2004). "Dangerous Supplements: Still At Large," *Consum. Rep. 69,* 12–17.

Consumer Reports (2010). "Dangerous Supplements: What You Don't Know About These 12 Ingredients Could Hurt You," *Consum. Rep. 75,* 16–20.

Costa, O.A., Axelsson, A., and Aniansson, G. (1988). "Hearing Loss at Age 7, 10 and 13: An Audiometric Follow-Up Study," *Scand. Audiol. Suppl. 30*, 25–32. PMID: 3227280.

Cruickshanks, K.J., Tweed, T.S., Wiley, T.L., Klein, B.E., Klein, R., Chappell, R., Nondahl, D.M., and Dalton, D.S. (2003). "The 5-Year Incidence and Progression of Hearing Loss: The Epidemiology of Hearing Loss Study," *Arch. Otolaryngol. Head Neck Surg. 129*, 1041–1046. doi: 10.1001/archotol.129.10.1041.

Curhan, S.G., Eavey, R., Shargorodsky, J., and Curhan, G.C. (2010). "Analgesic Use and the Risk of Hearing Loss in Men," *Am. J. Med. 123*, 231–237. doi: 10.1016/j.amjmed.2009.08.006.

Curhan, S.G., Eavey, R., Shargorodsky, J., and Curhan, G.C. (2011). "Prospective Study of Alcohol Use and Hearing Loss in Men," *Ear Hear. 32*, 46–52. doi: 10.1097/aud.0b013e3181f46a2f.

Curhan, S.G., Shargorodsky, J., Eavey, R., and Curhan, G.C. (2012). "Analgesic Use and the Risk of Hearing Loss in Women," *Am. J. Epidemiol. 176*, 544–554. doi: 10.1093/aje/kws146.

Curhan, S.G., Eavey, R., Wang, M., Stampfer, M.J., and Curhan, G.C. (2015). "Prospective Study of Alcohol Consumption and Self-Reported Hearing Loss in Women," *Alcohol 49*, 71–77. doi:10.1016/j.alcohol.2014.10.001.

Dagli, S. and Canlon, B. (1997). "The Effect of Repeated Daily Noise Exposure on Sound-Conditioned and Unconditioned Guinea Pigs," *Hear. Res. 104*, 39–46. doi: 10.1016/s0378-5955(96)00179-7.

Daniell, W.E., Swan, S.S., McDaniel, M.M., Camp, J.E., Cohen, M.A., and Stebbins, J.G. (2006). "Noise Exposure and Hearing Loss Prevention Programmes after 20 Years of Regulations in the United States," *Occup. Environ. Med. 63*, 343–351. doi: 10.1136/oem.2005.024588.

Davies, H.W., Teschke, K., Kennedy, S.M., Hodgson, M.R., and Demers, P.A. (2009) "Occupational Noise Exposure and Hearing Protector Use in Canadian Lumber Mills," *J. Occup. Environ. Hyg. 6*, 32–41. doi: 10.1080/15459620802548940.

Davies, H.W., Louie, A., Nahid, M., and Shoveller, J. (2012). "Potential Barriers to Engineered Noise Control in Food and Beverage Manufacturing in British Columbia, Canada: A Qualitative Study," *Int. J. Audiol. 51(Suppl 1)*, S43–50. doi: 10.3109/14992027.2011.633936.

Dawes, P., Cruickshanks, K.J., Moore, D.R., Edmondson-Jones, M., McCormack, A., Fortnum, H., and Munro, K.J. (2014). "Cigarette Smoking, Passive Smoking, Alcohol Consumption, and Hearing Loss," *J. Assoc. Res. Otolaryngol. 15*, 663–674. doi: 10.1007/s10162-014-0461-0.

Dobiasova, Z., Pazourek, J., and Havel, J. (2002). "Simultaneous Determination of Trans-Resveratrol and Sorbic Acid in Wine by Capillary Zone Electrophoresis," *Electrophoresis 23*, 263–267. doi: 10.1002/1522-2683(200202)23:2<263::aid-elps263>3.3.co;2-4.

Doosti, A., Lotfi, Y., Moossavi, A., Bakhshi, E., Talasaz, A.H., and Hoorzad, A. (2014). "Comparison of the Effects of N-Acetyl-Cysteine and Ginseng in Prevention of Noise Induced Hearing Loss in Male Textile Workers," *Noise Health 16*, 223–227. doi: 10.4103/1463-1741.137057.

Draper, T.H. and Bamiou, D.E. (2009). "Auditory Neuropathy in a Patient Exposed to Xylene: Case Report," *J. Laryngol. Otol. 123*, 462–465. doi: 10.1017/s0022215108002399.

Driscoll, D.P. and Royster, L.H. (1984). "Comparisons between the Median Hearing Threshold Levels for an Unscreened Black Nonindustrial Noise Exposed Population (NINEP) and Four Presbycusis Data Bases," *Am. Ind. Hyg. Assoc. J. 45*, 577–593. doi:10.1080/15298668491400304.

Du, X., Choi, C.H., Chen, K., Cheng, W., Floyd, R.A., and Kopke, R.D. (2011). "Reduced Formation of Oxidative Stress Biomarkers and Migration of Mononuclear Phagocytes in the Cochleae of Chinchilla after Antioxidant Treatment in Acute Acoustic Trauma," *Int. J. Otolaryngol. 2011*. 612690. doi: 10.1155/2011/612690.

Echt, K.V., Smith, S.L., Burridge, A.B., and Spiro, A. (2010). "Longitudinal Changes in Hearing Sensitivity among Men: The Veterans Affairs Normative Aging Study," *J. Acoust. Soc. Am. 128(4)*:1992–2002. doi: 10.1121/1.3466878.

Ecob, R., Sutton, G., Rudnicka, A., Smith, P., Power, C., Strachan, D., and Davis, A. (2008). "Is the Relation of Social Class to Change in Hearing Threshold Levels from Childhood to Middle Age Explained by Noise, Smoking, and Drinking Behaviour?" *Int. J. Audiol. 47*, 100–108. doi:10.1080/14992020701647942.

El-Shazly, A. (2006). "Toxic Solvents in Car Paints Increase the Risk of Hearing Loss Associated with Occupational Exposure to Moderate Noise Intensity," *B-ENT 2*, 1–5. PMID: 16676839.

Engström, J., Åstrand, I., and Wigaeus, E. (1978). "Exposure to Styrene in a Polymerization Plant: Uptake in the Organism and Concentration in Subcutaneous Adipose Tissue," *Scand. J. Work Environ. Health 4*, 324–329. doi: 10.5271/sjweh.2693.

Espin, J.C., Garcia-Conesa, M.T., and Tomas-Barberan, F.A. (2007). "Nutraceuticals: Facts and Fiction," *Phytochemistry 68*, 2986–3008. doi: 10.1016/j.phytochem.2007.09.014.

European Agency for Safety and Health at Work (2009). "Combined Exposure to Noise and Ototoxic Substances," Office for Official Publications of the European Communities, Luxembourg.

European Commission (2004). "Directive 2004/73/EC of 29 April 2004, Adapting to Technical Progress for the Twenty-Ninth Time Council. Directive 67/548/EEC on the Approximation of the Laws, Regulations and Administrative Provisions Relating to the Classification, Packaging and Labelling of Dangerous Substances, Annex I," *Off. J. Euro. Union L152/1*, 1–311.

European Parliament and the Council of the European Union (2003). "Directive 2003/10/EC, On the Minimum Health and Safety Requirements Regarding the Exposure of Workers to the Risks Arising from Physical Agents (Noise)," *Off. J. Euro. Union L42*, 38–44.

Ewert, D.L., Lu, J., Li, W., Du, X., Floyd, R., and Kopke, R. (2012). "Antioxidant Treatment Reduces Blast-Induced Cochlear Damage and Hearing Loss," *Hear. Res. 285,* 29–39. doi: 10.1016/j.heares.2012.01.013.

Faustman, E.M. and Omenn, G.S. (1996). "Risk Assessment," in *Casarett and Doull's Toxicology: The Basic Science of Poisons,* edited by C.D. Klaassen, McGraw-Hill, New York, 75–88.

Fechter, L.D. (2004). "Promotion of Noise-Induced Hearing Loss by Chemical Contaminants," *J. Toxicol. Environ. Health Part A 67(8-10),* 727–740. doi: 10.1080/15287390490428206.

Fechter, L.D., Thorne, P.R., and Nuttall, A.L. (1987). "Effects of Carbon Monoxide on Cochlear Electrophysiology and Blood Flow," *Hear. Res. 27,* 37–45.

Fechter, L.D., Young, J.S., and Carlisle, L. (1988). "Potentiation of Noise Induced Threshold Shifts and Hair Cell Loss by Carbon Monoxide," *Hear. Res. 34,* 39–47. doi: 10.1016/0378-5955(88)90049-4.

Fechter, L.D., Chen, G.D., and Johnson, D.L. (2002). "Potentiation of Noise-Induced Hearing Loss by Low Concentrations of Hydrogen Cyanide in Rats," *Toxicol. Sci. 66,* 131–138. doi: 10.1093/toxsci/66.1.131.

Fechter, L.D., Gearhart, C., Fulton, S., Campbell, J., Fisher, J., Na, K., Cocker, D., Nelson-Miller, A., Moon, P., and Pouyatos, B. (2007). "Promotion of Noise-Induced Cochlear Injury by Toluene and Ethylbenzene in the Rat," *Toxicol. Sci. 98,* 542–551. doi: 10.1093/toxsci/kfm109.

Fernandez, K.A., Jeffers, P.W., Lall, K., Liberman, M.C., and Kujawa, S.G. (2015). "Aging after Noise Exposure: Acceleration of Cochlear Synaptopathy in 'Recovered' Ears," *J. Neurosci. 35,* 7509–7520. doi: 10.1523/jneurosci.5138-14.2015.

Finley, J.W., Ellwood, K., and Hoadley, J. (2014). "Launching a New Food Product or Dietary Supplement in the United States: Industrial, Regulatory, and Nutritional Considerations," *Ann. Rev. Nutr. 34,* 421–447. doi: 10.1146/annurev-nutr-071813-105817.

Floyd, R.A., Kopke, R.D., Choi, C.H., Foster, S.B., Doblas, S., and Towner, R.A. (2008). "Nitrones as Therapeutics," *Free Radic. Biol. Med. 45,* 1361–1374. doi: 10.1016/j.freeradbiomed.2008.08.017.

Fox, D.J., Cooper, M.D., Speil, C.A., Roberts, M.H., Yanik, S.C., Meech, R.P., Hargrove, T.L., Verhulst, S.J., Rybak, L.P., and Campbell, K.C. (2015). "D-Methionine Reduces Tobramycin-Induced Ototoxicity without Antimicrobial Interference in Animal Models," *J. Cyst. Fibros. 15(4),* 518–530. doi: 10.1016/j.jcf.2015.06.005.

Fox, D., Harpring, G., Meech, R., Hargrove, T.L., Verhulst, S., Tischkau, S., and Campbell, K.C. (2016). "D-Methionine (D-Met) Influences Endogenous Antioxidant Activity and Lipid Peroxidation by Dose- and Tissue-Specific Mechanisms," *Abs. Assoc. Res. Otolaryngol. 39,* 381–382.

Fransen, E., et al. (2008). "Occupational Noise, Smoking, and a High Body Mass Index are Risk Factors for Age-Related Hearing Impairment and Moderate Alcohol Consumption is Protective: A European Population-Based Multicenter Study," *J. Assoc. Res. Otolaryngol. 9,* 264–276; discussion 261–263. doi: 10.1007/s10162-008-0123-1.

Fuente, A. and McPherson, B. (2007). "Central Auditory Processing Effects Induced by Solvent Exposure," *Int. J. Occup. Med. Environ. Health 20,* 271–279. doi: 10.2478/v10001-007-0030-4.

Furman, A.C., Kujawa, S.G., and Liberman, M.C. (2013). "Noise-Induced Cochlear Neuropathy Is Selective for Fibers with Low Spontaneous Rates," *J. Neurophysiol. 110,* 577–586. doi: 10.1152/jn.00164.2013.

Gopinath, B., Flood, V.M., McMahon, C.M., Burlutsky, G., Smith, W., and Mitchell, P. (2010). "The Effects of Smoking and Alcohol Consumption on Age-Related Hearing Loss: The Blue Mountains Hearing Study," *Ear Hear. 31,* 277–282. doi: 10.1097/aud.0b013e3181c8e902.

Gu, X., Creasy, L., Kester, A., and Zeece, M. (1999). "Capillary Electrophoretic Determination of Resveratrol in Wines," *J. Agric. Food Chem. 47,* 3223–3227. doi: 10.1021/jf981211e.

Guitton, M.J., Caston, J., Ruel, J., Johnson, R.M., Pujol, R., and Puel, J.L. (2003). "Salicylate Induces Tinnitus Through Activation of Cochlear NMDA Receptors," *J. Neurosci. 23,* 3944–3952. PMID: 12736364.

Guo, Y. and Bruno, R.S. (2015). "Endogenous and Exogenous Mediators of Quercetin Bioavailability," *J. Nutr. Biochem. 26,* 201–210. doi: 10.1016/j.jnutbio.2014.10.008.

Haddon, W., Jr. (1980). "Advances in the Epidemiology of Injuries as a Basis for Public Policy," *Public Health Rep. 95,* 411–421.

Halliwell, B. and Gutteridge, J.M.C. (2007). Free Radicals in *Biology and Medicine,* 4th edition, Oxford University Press, London.

Hamstra, D.A., Eisbruch, A., Naidu, M.U., Ramana, G.V., Sunkara, P., Campbell, K.C., Ross, B.D., and Rehemtulla, A. (2010). "Pharmacokinetic Analysis and Phase 1 Study of MRX-1024 in Patients Treated with Radiation Therapy with or without Cisplatinum for Head and Neck Cancer," *Clinical Cancer Research 16,* 2666–2676. doi: 10.1158/1078-0432.ccr-09-3318.

Hansen, B.G., Munn, S.J., Pakalin, S., Luotamo, M., Allanou, R., Pellegrini, G., De Bruijn, J., Berthault, F., Vegro, S., and Scheer, S. (2002). "EUR 20539 EN: European Union Risk Assessment Report," *Toluene 30,* 1–320.

Heinrich, U.R., Fischer, I., Brieger, J., Rumelin, A., Schmidtmann, I., Li, H., Mann, W.J., and Helling, K. (2008). "Ascorbic Acid Reduces Noise-Induced Nitric Oxide Production in the Guinea Pig Ear," *Laryngoscope 118,* 837–842. doi: 10.1097/mlg.0b013e31816381ae.

Henderson, D., Bielefeld, E.C., Harris, K.C., and Hu, B.H. (2006). "The Role of Oxidative Stress in Noise-Induced Hearing Loss," *Ear Hear. 27,* 1–19. doi: 10.1097/01.aud.0000191942.36672.f3.

Henderson, E., Testa, M.A., and Hartnick, C. (2011). "Prevalence of Noise-Induced Hearing-Threshold Shifts and Hearing Loss among U.S. Youths," *Pediatrics 127,* e39–46. doi: 10.1542/peds.2010-0926.

Henselman, L.W., Henderson, D., Subramaniam, M., and Sallustio, V. (1994). "The Effect of 'Conditioning' Exposures on Hearing Loss from Impulse Noise," *Hear. Res. 78,* 1–10. doi: 10.1016/0378-5955(94)90038-8.

Hickox, A.E. and Liberman, M.C. (2014). "Is Noise-Induced Cochlear Neuropathy Key to the Generation of Hyperacusis or Tinnitus?" *J. Neurophysiol. 111,* 552–564. doi: 10.1152/jn.00184.2013.

Hirata, M., Ogawa, Y., Okayama, A., and Goto, S. (1992). "A Cross-Sectional Study on the Brainstem Auditory Evoked Potential among Workers Exposed to Carbon Disulfide," *Int. Arch. Occup. Environ. Health. 64,* 321–324. doi: 10.1007/bf00379540.

Hodgkinson, L. and Prasher, D. (2006). "Effects of Industrial Solvents on Hearing and Balance: A Review," *Noise Health 8,* 114–133. doi: 10.4103/1463-1741.33952.

Hoet, P. and Lison, D. (2008). "Ototoxicity of Toluene and Styrene: State of Current Knowledge," *Crit. Rev. Toxicol. 38,* 127–170. doi: 10.1080/10408440701845443.

Holmes, A.E., Kaplan, H.S., Phillips, R.M., Kemker, F.J., Weber, F.T., and Isart, F.A. (1997). "Screening for Hearing Loss in Adolescents," *Speech-Language-Hearing in the Schools 28,* 70–75.

Holst, B. and Williamson, G. (2008). "Nutrients and Phytochemicals: From Bioavailability to Bioefficacy Beyond Antioxidants," *Curr. Opin. Biotechnol. 19,* 73–82. doi: 10.1016/j.copbio.2008.03.003.

Hwang, S.A., Gomez, M.I., Sobotova, L., Stark, A.D., May, J.J., and Hallman, E.M. (2001). "Predictors of Hearing Loss in New York Farmers," *Am. J. Ind. Med. 40,* 23–31. doi: 10.1002/ajim.1068.

Institute of Medicine. Dietary Reference Intakes (DRIs) (2004a). "Recommended Intakes for Individuals, Elements," Food and Nutrition Board, Institute of Medicine, National Academies of Science.

Institute of Medicine. Dietary Reference Intakes (DRIs) (2004b). "Recommended Intakes for Individuals, Vitamins," Food and Nutrition Board, Institute of Medicine, National Academies of Science.

Institute of Medicine. Dietary Reference Intakes (DRIs) (2004c). "Tolerable Upper Intake Levels (UL), Vitamins," Food and Nutrition Board, Institute of Medicine, National Academies of Science.

Institute of Medicine. Dietary Reference Intakes (DRIs) (2004d). "Tolerable Upper Intake Levels (UL), Elements," Food and Nutrition Board, Institute of Medicine, National Academies of Science.

International Labour Organization (2012). *Encyclopaedia of Occupational Health and Safety.*

Ishii, E.K. and Talbott, E.O. (1998). "Race/Ethnicity Differences in the Prevalence of Noise-Induced Hearing Loss in a Group of Metal Fabricating Workers," *J. Occup. Environ. Med. 40,* 661–666. doi: 10.1097/00043764-199808000-00001.

Itoh, A., Nakashima, T., Arao, H., Wakai, K., Tamakoshi, A., Kawamura, T., and Ohno, Y. (2001). "Smoking and Drinking Habits as Risk Factors for Hearing Loss in the Elderly: Epidemiological Study of Subjects Undergoing Routine Health Checks in Aichi, Japan," *Public Health 115,* 192–196. doi: 10.1016/s0033-3506(01)00442-5.

Jacobsen, P., Hein, H.O., Suadicani, P., Parving, A., and Gyntelberg, F. (1993). "Mixed Solvent Exposure and Hearing Impairment: An Epidemiological Study of 3284 Men: The Copenhagen Male Study," *Occup Med (Lond) 43,* 180–184. doi: 10.1093/occmed/43.4.180.

Jacono, A.A., Hu, B., Kopke, R.D., Henderson, D., Van De Water, T.R., and Steinman, H.M. (1998). "Changes in Cochlear Antioxidant Enzyme Activity after Sound Conditioning and Noise Exposure in the Chinchilla," *Hear. Res. 117,* 31–38. doi: 10.1016/s0378-5955(97)00214-1.

Jensen, J.B., Lysaght, A.C., Liberman, M.C., Qvortrup, K., and Stankovic, K.M. (2015). "Immediate and Delayed Cochlear Neuropathy after Noise Exposure in Pubescent Mice," *PLoS One 10:*e0125160. doi: 10.1371/journal.pone.0125160.

Jerger, J., Jerger, S., Pepe, P., and Miller, R. (1986). "Race Difference in Susceptibility to Noise-Induced Hearing Loss," *Am. J. Otol. 7,* 425–429. PMID: 3812644.

Joachims, Z., Netzer, A., Ising, H., Rebentisch, E., Attias, J., Weisz, G., and Gunther, T. (1993). "Oral Magnesium Supplementation As Prophylaxis for Noise-Induced Hearing Loss: Results of a Double Blind Field Study," *Schriftenr. Ver. Wasser. Boden. Lufthyg. 88,* 503–516. PMID: 8460390.

Johnson, A.C. (1992). "Auditory Sensitivity in Rats Exposed to Toluene and/or Acetyl Salicylic Acid," *Neuroreport. 3,* 1141–1144. doi: 10.1097/00001756-199212000-00028.

Johnson, A.C. and Canlon, B. (1994). "Progressive Hair Cell Loss Induced by Toluene Exposure," *Hear. Res. 75,* 201–208. doi: 10.1016/0378-5955(94)90071-x.

Johnson, A.C. and Morata, T.C. (2010). "Occupational Exposure to Chemicals and Hearing Impairment: The Nordic Expert Group for Criteria Documentation of Health Risks of Chemicals," *Arbete och Hälsa 44,* 1–77.

Kiely, K.M., Gopinath, B., Mitchell, P., Luszcz, M., and Anstey, K.J. (2012). "Cognitive, Health, and Sociodemographic Predictors of Longitudinal Decline in Hearing Acuity among Older Adults," *J. Gerontol. A. Biol. Sci. Med. Sci 67(9),* 997–1003. doi: 10.1093/gerona/gls066.

Kil, J., Lynch, E.D., Griffiths, S., Lobarinas, E., Spankovich, C., Antonelli, P.J., and Le Prell, C.G. (2014). "Efficacy of SPI-1005 for Prevention of Noise-Induced Hearing Loss: Phase 2 Clinical Trial Results," *Otolaryngol. Head Neck Surg. 151,* 83–84. doi: 10.1177/0194599814541627a172.

Kim, J., Park, H., Ha, E., Jung, T., Paik, N., and Yang, S. (2005). "Combined Effects of Noise and Mixed Solvents Exposure on the Hearing Function among Workers in the Aviation Industry," *Ind. Health 43,* 567–573. doi: 10.2486/indhealth.43.567.

Koga, K., Taguchi, A., Koshimizu, S., Suwa, Y., Yamada, Y., Shirasaka, N., and Yoshizumi, H. (2007). "Reactive Oxygen Scavenging Activity of Matured Whiskey and Its Active Polyphenols," *J. Food Sci. 72,* S212–217. doi: 10.1111/j.1750-3841.2007.00311.x.

Kolkhorst, F.W., Smaldino, J.J., Wolf, S.C., Battani, L.R., Plakke, B.L., Huddleston, S., and Hensley, L.D. (1998). "Influence of Fitness on Susceptibility to Noise-Induced Temporary Threshold Shift," *Med. Sci. Sports Exerc. 30,* 289–293. doi: 10.1097/00005768-199802000-00018.

Kopke, R.D., Jackson, R.L., Coleman, J.K.M., Liu, J., Bielefeld, E.C., and Balough, B.J. (2007). "NAC for Noise: From the Bench Top to the Clinic," *Hear. Res. 226,* 114–125. doi: 10.1016/j.heares.2006.10.008.

Kopke, R., Slade, M.D., Jackson, R., Hammill, T., Fausti, S., Lonsbury-Martin, B., Sanderson, A., Dreisbach, L., Rabinowitz, P., Torre, P., 3rd, and Balough, B. (2015). "Efficacy and Safety of N-Acetylcysteine in Prevention of Noise Induced Hearing Loss: A Randomized Clinical Trial," *Hear. Res. 323,* 40–50. doi: 10.1016/j.heares.2015.01.002.

Kramer, S., Dreisbach, L., Lockwood, J., Baldwin, K., Kopke, R.D., Scranton, S., and O'Leary, M. (2006). "Efficacy of the Antioxidant N-Acetylcysteine (NAC) in Protecting Ears Exposed to Loud Music," *J. Am. Acad. Audiol. 17,* 265–278. doi: 10.3766/jaaa.17.4.5.

Kujawa, S.G. and Liberman, M.C. (2006). "Acceleration of Age-Related Hearing Loss by Early Noise Exposure: Evidence of a Misspent Youth," *J. Neurosci. 26,* 2115–2123. doi: 10.1523/jneurosci.4985-05.2006.

Kujawa, S.G. and Liberman, M.C. (2009). "Adding Insult to Injury: Cochlear Nerve Degeneration after 'Temporary' Noise-Induced Hearing Loss," *J. Neurosci. 29,* 14077–14085. doi: 10.1523/jneurosci.2845-09.2009.

Lataye, R. and Campo, P. (1997). "Combined Effects of a Simultaneous Exposure to Noise and Toluene on Hearing Function," *Neurotoxicol. Teratol. 19,* 373–382. doi: 10.1016/s0892-0362(97)00049-4.

Lataye, R., Campo, P., and Loquet, G. (2000). "Combined Effects of Noise and Styrene Exposure on Hearing Function in the Rat," *Hear. Res. 139,* 86–96. doi: 10.1016/s0378-5955(99)00174-4.

Lataye, R., Campo, P., Loquet, G., and Morel, G. (2005). "Combined Effects of Noise and Styrene on Hearing: Comparison between Active and Sedentary Rats," *Noise Health 7,* 49–64. doi: 10.4103/1463-1741.31633.

Lataye, R., Maguin, K., and Campo, P. (2007). "Increase in Cochlear Microphonic Potential after Toluene Administration," *Hear. Res. 230,* 34–42. doi: 10.1016/j.heares.2007.04.002.

Laukli, E. and Hansen, P.W. (1995). "An Audiometric Test Battery for the Evaluation of Occupational Exposure to Industrial Solvents," *Acta Otolaryngol. 115,* 162–164. doi: 10.3109/00016489509139282.

Le Prell, C.G. (2016). "Current Issues in Clinical and Translational Research in the Hearing Sciences, Audiology, and Otolaryngology," in *Translational Research in Audiology and the Hearing Sciences, Springer Handbook of Auditory Research,* edited by C.G. Le Prell, E. Lobarinas, R.R. Fay, and A.N. Popper, Springer, New York, NY.

Le Prell, C.G. and Bao, J. (2012). "Prevention of Noise-Induced Hearing Loss: Potential Therapeutic Agents.," in *Noise-Induced Hearing Loss: Scientific Advances, Springer Handbook of Auditory Research,* edited by C.G. Le Prell, D. Henderson, R.R. Fay, and A.N. Popper, Springer Science+Business Media, LLC, New York, NY, 285–338.

Le Prell, C.G. and Lobarinas, E. (2015). "Strategies for Assessing Antioxidant Efficacy in Clinical Trials," in *Oxidative Stress in Applied Basic Research and Clinical Practice: Free Radicals in ENT Pathology,* edited by J.M. Miller, C.G. Le Prell, and L.P. Rybak, Humana Press, New York, NY, 163–192.

Le Prell, C.G. and Spankovich, C. (2013). "Noise-Induced Hearing Loss: Detection, Prevention and Management," in *Otology and Neurology,* edited by M.V. Kirtane, C.E. de Souza, M. Sanna, and A.K. Devaiah, Thieme, Stuttgart, Germany, 268–284.

Le Prell, C.G., Hughes, L.F., and Miller, J.M. (2007a). "Free Radical Scavengers Vitamins A, C, and E Plus Magnesium Reduce Noise Trauma," *Free Radic. Biol. Med. 42,* 1454–1463. doi: 10.1016/j.freeradbiomed.2007.02.008.

Le Prell, C.G., Yamashita, D., Minami, S., Yamasoba, T., and Miller, J.M. (2007b). "Mechanisms of Noise-Induced Hearing Loss Indicate Multiple Methods of Prevention," *Hear. Res. 226,* 22–43. doi: 10.1016/j.heares.2006.10.006.

Le Prell, C.G., Johnson, A.-C., Lindblad, A.-C., Skjönsberg, A., Ulfendahl, M., Guire, K., Green, G.E., Campbell, K.C.M., and Miller, J.M. (2011). "Increased Vitamin Plasma Levels in Swedish Military Personnel Treated with Nutrients Prior to Automatic Weapon Training," *Noise Health 13,* 432–443. doi: 10.4103/1463-1741.90317.

Le Prell, C.G., Fulbright, A., Spankovich, C., Griffiths, S., Lobarinas, E., Campbell, K.C.M., Antonelli, P.J., Green, G.E., Guire, K., and Miller, J.M. (2016). "Dietary Supplement Comprised of β-Carotene, Vitamin C, Vitamin E, and Magnesium: Failure to Prevent Music-Induced Temporary Threshold Shift," Audiology and Neurotology *EXTRA 6,* 20–39. doi: 10.1159/000446600.

Lee, F.S., Matthews, L.J., Dubno, J.R., and Mills, J.H. (2005). "Longitudinal Study of Pure-Tone Thresholds in Older Persons," *Ear Hear. 26,* 1–11. doi: 10.1097/00003446-200502000-00001.

Li, H.S., Johnson, A.C., Borg, E., and Höglund, G. (1992). "Auditory Degeneration after Exposure to Toluene in Two Genotypes of Mice," *Arch. Toxicol. 66,* 382–386. doi: 10.1007/bf02035126.

Lim, D.J. and Melnick, W. (1971). "Acoustic Damage of the Cochlea: A Scanning and Transmission Electron Microscopic Observation," *Arch. Otolaryngol. 94,* 294–305. doi: 10.1001/archotol.1971.00770070486002.

Lin, C.Y., Wu, J.L., Shih, T.S., Tsai, P.J., Sun, Y.M., Ma, M.C., and Guo, Y.L. (2010). "N-Acetyl-Cysteine Against Noise-Induced Temporary Threshold Shift in Male Workers," *Hear. Res. 269,* 42–47. doi: 10.1016/j.heares.2010.07.005.

Lin, H.W., Furman, A.C., Kujawa, S.G., and Liberman, M.C. (2011). "Primary Neural Degeneration in the Guinea Pig Cochlea after Reversible Noise-Induced Threshold Shift," *J. Assoc. Res. Otolaryngol. 12,* 605–616. doi: 10.1007/s10162-011-0277-0.

Lindblad, A.C., Rosenhall, U., Olofsson, A., and Hagerman, B. (2011). "The Efficacy of N-Acetylcysteine to Protect the Human Cochlea from Subclinical Hearing Loss Caused by Impulse Noise: A Controlled Trial," *Noise Health 13,* 392–401. doi: 10.4103/1463-1741.90293.

Lindgren, F. and Axelsson, A. (1988). "The Influence of Physical Exercise on Susceptibility to Noise-Induced Temporary Threshold Shift," *Scand Audiol 17,* 11–17. doi: 10.3109/01050398809042175.

Lo, W.C., Liao, L.J., Wang, C.T., Young, Y.H., Chang, Y.L., and Cheng, P.W. (2013). "Dose-Dependent Effects of D-Methionine for Rescuing Noise-Induced Permanent Threshold Shift in Guinea-Pigs," *Neuroscience 254,* 222–229. doi: 10.1016/j.neuroscience.2013.09.027.

Loquet, G., Campo, P., and Lataye, R. (1999). "Comparison of Toluene-Induced and Styrene-Induced Hearing Losses," *Neurotoxicol. Teratol. 21,* 689–697. doi: 10.1016/s0892-0362(99)00030-6.

Lu, J., Li, W., Du, X., Ewert, D.L., West, M.B., Stewart, C., Floyd, R.A., and Kopke, R.D. (2014). "Antioxidants Reduce Cellular and Functional Changes Induced by Intense Noise in the Inner Ear and Cochlear Nucleus," *J. Assoc. Res. Otolaryngol. 15,* 353–372. doi: 10.1007/s10162-014-0441-4.

Lund, S.P. and Kristiansen, G.B. (2008). "Hazards to Hearing from Combined Exposure to Toluene and Noise in Rats," *Int. J. Occup. Med. Environ Health. 21,* 47–57. doi: 10.2478/v10001-008-0008-x.

Magalhaes, P.J., Carvalho, D.O., Cruz, J.M., Guido, L.F., and Barros, A.A. (2009). "Fundamentals and Health Benefits of Xanthohumol, A Natural Product Derived from Hops and Beer," *Nat. Prod. Commun. 4,* 591–610. PMID: 19445313.

Maguin, K., Campo, P., and Parietti-Winkler, C. (2009). "Toluene Can Perturb the Neuronal Voltage-Dependent Ca2+ Channels Involved in the Middle-Ear Reflex," *Toxicol. Sci. 107,* 473–481. doi: 10.1093/toxsci/kfn242.

Mäkitie, A.A., Pirvola, U., Pyykko, I., Sakakibara, H., Riihimaki, V., and Ylikoski, J. (2003). "The Ototoxic Interaction of Styrene and Noise," *Hear. Res. 179,* 9–20. doi: 10.1016/s0378-5955(03)00066-2.

Manson, J., Alessio, H.M., Cristell, M., and Hutchinson, K.M. (1994). "Does Cardiovascular Health Mediate Hearing Ability?" *Med. Sci. Sports Exerc. 26,* 866–871. doi: 10.1249/00005768-199407000-00009.

McClements, D.J., Li, F., and Xiao, H. (2015). "The Nutraceutical Bioavailability Classification Scheme: Classifying Nutraceuticals According to Factors Limiting Their Oral Bioavailability," *Annual Rev. of Food Sci. and Technol. 6,* 299–327. doi: 10.1146/annurev-food-032814-014043.

McFadden, S.L., Henderson, D., and Shen, Y.H. (1997). "Low-Frequency 'Conditioning' Provides Long-Term Protection from Noise-Induced Threshold Shifts in Chinchillas," *Hear. Res. 103,* 142–150. doi: 10.1016/s0378-5955(96)00170-0.

McFadden, S.L., Henselman, L.W., and Zheng, X.Y. (1999). "Sex Differences in Auditory Sensitivity of Chinchillas Before and After Exposure to Impulse Noise," *Ear Hear. 20,* 164–174. doi: 10.1097/00003446-199904000-00007.

McWilliams, M.L., Chen, G.D., and Fechter, L.D. (2000). "Low-Level Toluene Disrupts Auditory Function in Guinea Pigs," *Toxicol. Appl. Pharmacol. 167,* 18–29. doi: 10.1006/taap.2000.8978.

Meszka-Jordan, A., Mahlapuu, R., Soomets, U., and Carlson, G.P. (2009). "Oxidative Stress Due to (R)-Styrene Oxide Exposure and the Role of Antioxidants in Non-Swiss Albino (NSA) Mice," *J. Toxicol. Environ. Health A 72,* 642–650. doi: 10.1080/15287390902769436.

Metwally, F.M., Aziz, H.M., Mahdy-Abdallah, H., Elgelil, K.S., and El-Tahlawy, E.M. (2012). "Effect of Combined Occupational Exposure to Noise and Organic Solvents on Hearing," *Toxicol. Ind. Health 28,* 901–907. doi: 10.1177/0748233711427051.

Ministério da Previdência e Assistência (1999). Social Decree 3048 Aprova o Regulamento da Previdência Social, e dá Outras Providências, Brazil: Diário Oficial da União, April 12, 1999 (in Portuguese).

Ministre du Travail de l'emploi et de la santé (2012). Décret n° 2012-746 du 9 mai 2012 Fixant des Valeurs Limites d'Exposition Professionnelle Contraignantes Pour Certains Agents Chimiques. http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000025836934&fastPos=1&fastReqId=1200810400&categorieLien=cid&oldAction=rechTexte

Mizoue, T., Miyamoto, T., and Shimizu, T. (2003). "Combined Effect of Smoking and Occupational Exposure to Noise on Hearing Loss in Steel Factory Workers," *Occup. Environ. Med. 60,* 56–59. doi: 10.1136/oem.60.1.56.

Moen, B.E., Riise, T., and Kyvik, K.R. (1999). "P300 Brain Potential among Workers Exposed to Organic Solvents," *Norsk Epidemiologi. 9:*27–31. doi: 10.5324/nje.v9i1.439.

Mohammadi, S., Labbafinejad, Y., and Attarchi, M. (2010). "Combined Effects of Ototoxic Solvents and Noise on Hearing in Automobile Plant Workers in Iran," *Arh. Hig. Rada. Toksikol. 61,* 267–274 (2010). doi: 10.2478/10004-1254-61-2010-2013.

Morata, T.C. (1989). "Study of the Effects of Simultaneous Exposure to Noise and Carbon Disulfide on Workers' Hearing," *Scand. Audiol. 18,* 53–58. doi: 10.3109/01050398909070723.

Morata, T.C. (2003). "Chemical Exposure as a Risk Factor for Hearing Loss," *J. Occup. Environ. Med. 45,* 676–682. doi: 10.1097/01.jom.0000071507.96740.70.

Morata, T.C. and Lemasters, G.K. (1995). "Epidemiologic Considerations in the Evaluation of Occupational Hearing Loss," *Occup. Med. 10,* 641–656. PMID: 8578424.

Morata, T.C., Dunn, D.E., Kretschmer, L.W., Lemasters, G.K., and Keith, R.W. (1993). "Effects of Occupational Exposure to Organic Solvents and Noise on Hearing," *Scand. J. Work Environ. Health 19,* 245–254 (1993). doi: 10.5271/sjweh.1477.

Morata, T.C., Engel, T., Durao, A., Costa, T.R., Krieg, E.F., D.E., Dunn, and Lozano, M.A. (1997a). "Hearing Loss from Combined Exposures among Petroleum Refinery Workers," *Scand. Audiol. 26,*141–149. doi: 10.3109/01050399709074987.

Morata, T.C., Fiorini, A.C., Fischer, F.M., Colacioppo, S., Wallingford, K.M., Krieg, E.F., Dunn, D.E., Gozzoli, L., Padrao, M.A., and Cesar, C.L. (1997b). "Toluene-Induced Hearing Loss among Rotogravure Printing Workers," *Scand. J. Work Environ. Health 23,* 289–298. doi: 10.5271/sjweh.222.

Morata, T.C., Johnson, A.C., Nylen, P., Svensson, E.B., Cheng, J., Krieg, E.F., Lindblad, A.C., Ernstgard, L., and Franks, J. (2002). "Audiometric Findings in Workers Exposed to Low Levels of Styrene and Noise," *J. Occup. Environ. Med. 44,* 806–814. doi: 10.1097/00043764-200209000-00002.

Morata, T.C., Sliwinska-Kowalska, M., Johnson, A.C., Starck, J., Pawlas, K., Zamyslowska-Szmytke, E., Nylen, P., Toppila, E., Krieg, E., Pawlas, N., and Prasher, D. (2011). "A Multicenter Study on the Audiometric Findings of Styrene-Exposed Workers," *Int. J. Audiol. 50(10),* 652–660. doi: 10.3109/14992027.2011.588965.

Morrell, C.H., Gordon-Salant, S., Pearson, J.D., Brant, L.J., and Fozard, J.L. (1996). "Age- and Gender-Specific Reference Ranges for Hearing Level and Longitudinal Changes in Hearing Level," *J. Acoust. Soc. Am. 100,* 1949–1967. doi: 10.1121/1.417906.

Morton, C.C. and Nance, W.E. (2006). "Newborn Hearing Screening: A Silent Revolution," *N. Engl. J. Med. 354,* 2151–2164. doi: 10.1056/nejmra050700.

Motalebi Kashani, M., Saberi, H., and Hannani, M. (2013). "Prevention of Acoustic Trauma-Induced Hearing Loss by N-Acetylcysteine Administration in Rabbits," *Arch. Trauma Res. 1,* 145–150. doi: 10.5812/atr.7839.

National Cancer Institute (2005). *Theory at a Glance: A Guide for Health Promotion Practice,* U.S. Department of Health and Human Services, National Institutes of Health, Washington, D.C.

NCT00808470. Micronutrients to Prevent Noise-induced Hearing Loss. http://clinicaltrials.gov/ct2/show/NCT00808470

NCT01444846. Otoprotection with SPI-1005 [Online] http://clinicaltrials.gov/ct2/show/NCT01444846.

Nicotera, T.M., Henderson, D., Zheng, X.Y., Ding, D.L., and McFadden, S.L. (1999). "Reactive Oxygen Species, Apoptosis, and Necrosis in Noise-Exposed Cochleas of Chinchillas," *Abs. Assoc. Res. Otolaryngol. 22,* 159.

Niklasson, M., Arlinger, S., Ledin, T., Moller, C., Odkvist, L., Flodin, U., and Tham, R. (1998). "Audiological Disturbances Caused by Long-Term Exposure to Industrial Solvents. Relation to the Diagnosis of Toxic Encephalopathy," *Scand. Audiol. 27,* 131–136. doi: 10.1080/010503998422629.

NIOSH (1996). *Preventing Occupational Hearing Loss: A Practical Guide,* DHHS (NIOSH) Pub. No. 96-110, Natl. Inst. for Occup. Safety and Health, Cincinnati, OH.

NIOSH (1998). *Criteria for a Recommended Standard: Occupational Noise Exposure,* Revised criteria, DHHS (NIOSH) Pub. No. 98-126, Natl. Inst. for Occup. Safety and Health, Cincinnati, OH.

Niskar, A.S., Kieszak, S.M., Holmes, A.E., Esteban, E., Rubin, C., and Brody, D.J. (2001). "Estimated Prevalence of Noise-Induced Hearing Threshold Shifts among Children 6 to 19 Years of Age: The Third National Health and Nutrition Examination Survey, 1988-1994, United States," *Pediatrics 108,* 40–43. doi: 10.1542/peds.108.1.40.

Ödkvist, L.M., Arlinger, S.D., Edling, C., Larsby, B., and Bergholtz, L.M. (1987). "Audiological and Vestibulo-Oculomotor Findings in Workers Exposed to Solvents and Jet Fuel," *Scand. Audiol. 16,* 75–81. doi: 10.3109/01050398709042159.

Ödkvist, L.M., Moller, C., and Thuomas, K.A. (1992). "Otoneurologic Disturbances Caused by Solvent Pollution," *Otolaryngol. Head Neck Surg. 106,* 687–692.

Ohinata, Y., Miller, J.M., Altschuler, R.A., and Schacht, J. (2000). "Intense Noise Induces Formation of Vasoactive Lipid Peroxidation Products in The Cochlea," *Brain Research 878,* 163–173. doi: 10.1016/s0006-8993(00)02733-5.

Ohlemiller, K.K., Wright, J.S., and Dugan, L.L. (1999). "Early Elevation of Cochlear Reactive Oxygen Species Following Noise Exposure," *Audiol. Neurotol. 4,* 229–236. doi: 10.1159/000013846.

Ohlemiller, K.K., Wright, J.S., and Heidbreder, A.F. (2000). "Vulnerability to Noise-Induced Hearing Loss in 'Middle-Aged' and Young Adult Mice: A Dose-Response Approach in CBA, C57BL, and BALB Inbred Strains," *Hear. Res. 149,* 239–247. doi: 10.1016/s0378-5955(00)00191-x.

OSHA (1983). "Occupational Noise Exposure; Hearing Conservation Amendment; Final Rule," Occup. Safety and Health Admin., 29 CFR1910.95 *Fed. Regist. 48(46),* 9738-9785.

OSHA/NIOSH (2018). "Preventing Hearing Loss Caused by Chemical (Ototoxicity) and Noise Exposure," Safety and Health Information Bulletin, SHIB 03-08-2018, DHHS (NIOSH) Pub. No. 2018-124, Natl. Inst. for Occup. Safety and Health, Cincinnati, OH.

Ostri, B. and Parving, A. (1991). "A Longitudinal Study of Hearing Impairment in Male Subjects: An 8-Year Follow-Up," *Br. J. Audiol. 25,* 41–48. doi: 10.3109/03005369109077863.

Ozkul, Y., Songu, M., Basoglu, M.S., Ozturkcan, S., and Katilmis, H. (2014). "Evaluation of the Protective Effect of Alpha-Lipoic Acid on Cisplatin Ototoxicity Using Distortion-Product Otoacoustic Emission Measurements: An Experimental Animal Study," *J. Craniofac. Surg. 25,* :1515–1518. doi: 10.1097/scs.0000000000000881.

Patel, R.P., McAndrew, J., Sellak, H., White, C.R., Jo, H., Freeman, B.A., and Darley-Usmar, V.M. (1999). "Biological Aspects of Reactive Nitrogen Species," *Biochim. Biophys. Acta 1411,* 385–400. doi: 10.1016/s0005-272899)00028-6.

Patino, R. (2009). "Intellectual Property Rights and Research Disclosure in the University Environment: Preserving The Commercialization Option And Optimizing Market Interest," *J. Am. Assoc. Lab. Animal Sci. 48,* 138–143. PMCID: PMC2679667.

Pawlaczyk-Luszczynska, M., Dudarewicz, A., Zamojska, M., and Sliwinska-Kowalska, M. (2012). "Self-Assessment of Hearing Status and Risk of Noise-Induced Hearing Loss in Workers in a Rolling Stock Plant," *Int. J. Occup. Saf. Ergon. 18,* 279–296. doi: 10.1080/10803548.2012.11076934.

Pearson, J.D., Morrell, C.H., Gordon-Salant, S., Brant, L.J., Metter, E.J., Klein, L.L., and Fozard, J.L. (1995). "Gender Differences in a Longitudinal Study of Age-Associated Hearing Loss," *J. Acoust. Soc. Am. 97,* 1196–1205. doi: 10.1121/1.412231.

Poirrier, A.L., Pincemail J., Van Den Ackerveken, P., Lefebvre, P.P., and Malgrange, B. (2010). "Oxidative Stress in the Cochlea: An Update," *Curr. Med. Chem. 17,* 3591–3604. doi: 10.2174/092986710792927895.

Pollastrini, L., Abramo, A., Cristalli, G., Baretti, F., and Greco, A. (1994). "Early Signs of Occupational Ototoxicity Caused by Inhalation of Benzene Derivative Industrial Solvents," *Acta Otorhinolaryngol. Ital. 14,* 503–512. PMID: 7956451.

Pouyatos, B., Gearhart, C.A., and Fechter, L.D. (2005). "Acrylonitrile Potentiates Hearing Loss and Cochlear Damage Induced by Moderate Noise Exposure in Rats," *Toxicol. Appl. Pharmacol. 204,* 46–56. doi: 10.1016/j.taap.2004.08.015.

Prasher, D., Morata, T., Campo, P., Fechter, L., Johnson, A.C., Lund, S.P., Pawlas, K., Starck, J., Sulkowski, W., and Sliwinska-Kowalska, M. (2002). "Noisechem: An European Commission Research Project on the Effects of Exposure to Noise and Industrial Chemicals on Hearing and Balance," *Int. J. Occup. Med. Environ. Health. 15,* 5–11. PMID: 12678927.

Pukkila, M., Zhai, S., Virkkala, J., Pirvola, U., and Ylikoski, J. (1997). "The 'Toughening' Phenomenon in Rat's Auditory Organ," *Acta Otolaryngol. Suppl. (Stockh). 529,* 59–62. doi: 10.3109/00016489709124081.

Quaranta, N., Dicorato, A., Matera, V., D'Elia, A., and Quaranta, A. (2012). "The Effect of Alpha-Lipoic Acid on Temporary Threshold Shift in Humans: A Preliminary Study," *Acta Otorhinolaryngol. Ital. 32,* 380–385. PMID: 23349557.

Rabinowitz, P.M., Pierce Wise, J., Sr., Hur Mobo, B., Antonucci, P.G., Powell, C., and Slade, M. (2002). "Antioxidant Status and Hearing Function in Noise-Exposed Workers," *Hear. Res. 173,* 164–171. PMID: 12372644.

Rao, D. and Fechter, L.D. (2000a). "Protective Effects of Phenyl-N-Tert-Butylnitrone on the Potentiation of Noise-Induced Hearing Loss by Carbon Monoxide," *Toxicol. Appl. Pharmacol. 167,* 125–131. doi: 10.1006/taap.2000.8995.

Rao, D. and Fechter, L.D. (2000b). "Increased Noise Severity Limits Potentiation of Noise Induced Hearing Loss by Carbon Monoxide," *Hear. Res. 150,* 206–214. doi: 10.1016/s0378-5955(00)00202-1.

Reddy, R.K., Welch, D., Thorne, P., and Ameratunga, S. (2012). "Hearing Protection Use in Manufacturing Workers: A Qualitative Study," *Noise Health 14,* 202–209. doi: 10.4103/1463-1741.99896.

Rewerska, A., Pawelczyk, M., Rajkowska, E., Politanski, P., and Sliwinska-Kowalska, M. (2013). "Evaluating D-Methionine Dose to Attenuate Oxidative Stress-Mediated Hearing Loss Following Overexposure to Noise," *Eur. Arch. Otorhinolaryngol. 270,* 1513–1520. doi: 10.1007/s00405-012-2265-3.

Rybak, L.P. and Somani, S. (1999). "Ototoxicity: Amelioration by Protective Agents," *Ann. N.Y. Acad. Sci. 884,* 143–151. PMID: 10220857.

Rybak, L.P., Husain, K., Whitworth, C., and Somani, S.M. (1999). Dose Dependent Protection by Lipoic Acid against Cisplatin-Induced Ototoxicity in Rats: Antioxidant Defense System," *Toxicol. Sci. 47,* 195–202.

Schacht, J. and Hawkins, J.E. (2006). "Sketches of Otohistory, Part 11: Ototoxicity: Drug-Induced Hearing Loss," *Audiol. Neurotol. 11,* 1–6. doi: 10.1159/000088850.

Schäper, M., Seeber, A., and van Thriel, C. (2008). "The Effects of Toluene Plus Noise on Hearing Thresholds: An Evaluation Based on Repeated Measurements in the German Printing Industry," *Int. J. Occup. Med. Environ. Health 21,* 191–200. doi: 10.2478/v10001-008-0030-z.

Seifried, H.E., Anderson, D.E., Fisher, E.I., and Milner, J.A. (2007). "A Review of the Interaction among Dietary Antioxidants and Reactive Oxygen Species," *J. Nutritional Biochem. 18,* 567–579. doi: 10.1016/j.jnutbio.2006.10.007.

Sekhar, D.L., Rhoades, J.A., Longenecker, A.L., Beiler, J.S., King, T.S., Widome, M.D., and Paul, I.M. (2011). "Improving Detection of Adolescent Hearing Loss," *Arch. Pediatr. Adolesc. Med. 165,* 1094–1100. doi: 10.1001/archpediatrics.2011.188.

Sha, S.H., Qiu, J.H., and Schacht, J. (2006). "Aspirin to Prevent Gentamicin-Induced Hearing Loss," *N. Engl. J. Med. 354,* 1856–1857. doi: 10.1056/NEJMc053428.

Sharabi, Y., Reshef-Haran, I., Burstein, M., and Eldad, A. (2002). "Cigarette Smoking and Hearing Loss: Lessons from the Young Adult Periodic Examinations in Israel (YAPEIS) Database," *Isr. Med. Assoc. J. 4,* 1118–1120. PMID: 12516904.

Sheppard, A., Hayes, S.H., Chen, G.D., Ralli, M., and Salvi, R. (2014). "Review of Salicylate-Induced Hearing Loss, Neurotoxicity, Tinnitus and Neuropathophysiology," *Acta Otorhinolaryngol. Ital. 34,* 79–93. PMID: 24843217.

Shi, X. and Nuttall, A.L. (2003). "Upregulated iNOS and Oxidative Damage to the Cochlear Stria Vascularis Due to Noise Stress," *Brain Research 967,* 1–10. PMID: 12650960.

Sliwinska-Kowalska, M. (2007). "Exposure to Organic Solvent Mixture and Hearing Loss: Literature Overview," *Int. J. Occup. Med. Environ. Health 20,* 309–314. PMID: 18516812.

Sliwinska-Kowalska, M., Zamyslowska-Szmytke, E., Szymczak, W., Kotylo, P., Fiszer, M., Dudarewicz, A., Wesolowski, W., Pawlaczyk-Luszczynska, M., and Stolarek, R. (2001). "Hearing Loss among Workers Exposed to Moderate Concentrations of Solvents," *Scand. J. Work Environ. Health 27,* 335–342. PMID: 11712614.

Sliwinska-Kowalska, M., Zamyslowska-Szmytke, E., Szymczak, W., Kotylo, P., Fiszer, M., Wesolowski, W., and Pawlaczyk-Luszczynska, M. (2003). "Ototoxic Effects of Occupational Exposure to Styrene and Co-Exposure to Styrene and Noise," *J. Occup. Environ. Med. 45,* 15–24. PMID: 12553175.

Sliwinska-Kowalska, M., Prasher, D., Rodrigues, C.A., Zamyslowska-Szmytke, E., Campo, P., Henderson, D., Lund, S.P., Johnson, A.C., Schaper, M., Odkvist, L., Starck, J., Toppila, E., Schneider, E., Moller, C., Fuente, A., and Gopal, K.V. (2007). "Ototoxicity of Organic Solvents: From Scientific Evidence to Health Policy," *Int. J. Occup. Med. Environ. Health 20,* 215–222. doi: 10.2478/v10001-007-0021-5.

Smith, A.W. (1998). "The World Health Organisation and the Prevention of Deafness and Hearing Impairment Caused by Noise," *Noise Health 1,* 6–12. PMID: 12689363.

Spankovich, C. and Le Prell, C.G. (2013). "Healthy Diets, Healthy Hearing: National Health and Nutrition Examination Survey, 1999-2002," *Int. J. Audiol. 52,* 369–276. doi: 10.3109/14992027.2013.780133.

Spankovich, C. and Le Prell, C.G. (2014). "Associations between Dietary Quality, Noise, and Hearing: Data from the National Health and Nutrition Examination Survey, 1999–2002," *Int. J. Audiol. 53,* 796–809. doi: 10.3109/14992027.2014.921340.

Starck, J., Toppila, E., and Pyykkö, I. (1999). "Smoking as a Risk Factor in Sensory Neural Hearing Loss among Workers Exposed to Occupational Noise," *Acta Otolaryngol. 11,* 302–305. PMID: 10380732.

Steinhauer, S.R., Morrow, L.A., Condray, R., and Dougherty, G.G. (1997). "Event-Related Potentials in Workers with Ongoing Occupational Exposure," *Biol. Psychiatry 42,* 854–858. PMID: 9347137.

Subramaniam, M., Henderson, D., Campo, P., and Spongr, V. (1992). "The Effect of 'Conditioning' on Hearing Loss from a High Frequency Traumatic Exposure," *Hear. Res. 58*:57–62. PMID: 1559906.

Subramaniam, M., Henderson, D., and Spongr V. (1993). "Effect of Low-Frequency 'Conditioning' on Hearing Loss from High-Frequency Exposure," *J. Acoust. Soc. Am. 93,* 952–956. PMID: 8445129.

Sulkowski, W.J., Kowalska, S., Matyja, W., Guzek, W., Wesolowski, W., Szymczak, W., and Kostrzewski, P. (2002). "Effects of Occupational Exposure to a Mixture of Solvents on the Inner Ear: A Field Study," *Int. J. Occup. Med. Environ. Health. 15,* 247–256. PMID: 12462452.

Sullivan, M.J., Rarey, K.E., and Conolly, R.B. (1988). "Ototoxicity of Toluene in Rats," *Neurotoxicol. Teratol. 10,* 525–530. PMID: 3244344.

Suter, A.H. (2009). "The Hearing Conservation Amendment: 25 Years Later," *Noise Health 11,* 2–7. PMID: 19265247.

Szanto, C. and Ionescu, M. (1983). "Influence of Age and Sex on Hearing Threshold Levels in Workers Exposed to Different Intensity Levels of Occupational Noise," *Audiology 22,* 339–356. PMID: 6615339.

Tak, S., Davis, R.R., and Calvert, G.M. (2009). "Exposure to Hazardous Workplace Noise and Use of Hearing Protection Devices among U.S. Workers, NHANES, 1999–2004," *Am. J. Ind. Med. 52,* 358–371. doi: 10.1002/ajim.20690.

Tikka, C., Verbeek, J.H., Kateman, E., Morata, T.C., Dreschler, W.A., and Ferrite, S. (2017). "Interventions to Prevent Occupational Noise-Induced Hearing Loss," *Cochrane Database of Systematic Rev. 7,* CD006396. doi: 10.1002/14651858.CD006396.pub4

Toppila, E., Pyykko, I.I., Starck, J., Kaksonen, R., and Ishizaki, H. (2000). "Individual Risk Factors in the Development of Noise-Induced Hearing Loss," *Noise Health 2,* 59–70. PMID: 12689463.

Toppila, E., Starck, J., Pyykko, I., and Miller, J.M. (2002). Protection Against Acute Noise with Antioxidants, presented at Nordic Noise: An International Symposium on Noise and Health, in Nobel Forum, Karolinska Institutet, Stockholm, Sweden.

U.S. Army Center for Health Promotion and Preventive Medicine (2003). Occupational Ototoxins (Ear Poisons) and Hearing Loss, Fact sheet 51-002-0903. https://phc.amedd.army.mil/PHC%20Resource%20Library/Ototoxin_FS_51-002-0713.pdf

U.S. Department of the Army (1998). Medical Services: Hearing Conservation Program, Pamphlet 40-501.

Upile, T., Sipaul, F., Jerjes, W., Singh, S., Nouraei, S.A., El Maaytah, M., Andrews, P., Graham, J., Hopper, C., and Wright, A. (2007). "The Acute Effects of Alcohol on Auditory Thresholds," *BMC Ear, Nose, and Throat Disorders 7,* 4. doi: 10.1186/1472-6815-7-4.

Varney, N.R., Morrow, L.A., Pinkston, J.B., and Wu, J.C. (1998). "PET Scan Findings in a Patient with a Remote History of Exposure to Organic Solvents," *Appl. Neuropsychol. 5,* 100–106. doi: 10.1207/s15324826an0502_6.

Venet, T., Rumeau, C., Campo, P., Rieger, B., Thomas, A., and Cour, C. (2011). "Neuronal Circuits Involved in the Middle-Ear Acoustic Reflex," *Toxicol. Sci. 119,* 146–155. doi: 10.1093/toxsci/kfq312.

Venet, T., P. Campo, A. Thomas, C. Cour, B. Rieger, and F. Cosnier (2015). "The Tonotopicity of Styrene-Induced Hearing Loss Depends on the Associated Noise Spectrum," *Neurotoxicol. Teratol. 48,*56–63. doi: 10.1016/j.ntt.2015.02.003.

Vrca, A., Karacic, V., Bozicevic, D., Bozikov, V., and Malinar M. (1996). "Brainstem Auditory Evoked Potentials in Individuals Exposed to Long-Term Low Concentrations of Toluene," *Am. J. Ind. Med. 30,* 62–66. doi: 10.1002/(SICI)1097-0274(199607)30:1<62::AID-AJIM10>3.0.CO;2-6.

Vyskocil, A., Leroux, T., Truchon, G., Gendron, M., El Majidi, N., and Viau, C. (2008a). "Occupational Ototoxicity of N-Hexane," *Hum. Exp. Toxicol. 27,* 471–476. doi: 10.1177/0960327108093719.

Vyskocil, A., Leroux, T., Truchon, G., Lemay, F., Gendron, M., Gagnon, F., El Majidi, N., and Viau, C. (2008b). "Ethyl Benzene Should be Considered Ototoxic at Occupationally Relevant Exposure Concentrations," *Toxicol. Ind. Health 24,* 241–246. doi: 10.1177/0748233708094097.

Vyskocil A., Truchon, G., Leroux, T., Lemay, F., Gendron, M., Gagnon, F., Botez, S., El Majidi, N., Lim, S., Emond, C., Viau, C. (2009). *Ototoxic Potential of Industrial Chemicals.* http://www.irsst.qc.ca/en/.

Wang, A., Hou, N., Bao, D., Liu, S., and Xu, T. (2012). "Mechanism of Alpha-Lipoic Acid in Attenuating Kanamycin-Induced Ototoxicity," *Neural Regeneration Res. 7,* 2793–2800. doi: 10.3969/j.issn.1673-5374.2012.35.007.

Webb, G.P. (2007). "Nutritional Supplements and Conventional Medicine: What Should the Physician Know?" *Proc. Nutr. Soc. 66,* 471–478. doi: 10.1017/S0029665107005782.

Wild, D.C., Brewster, M.J., and Banerjee, A.R. (2005). "Noise-Induced Hearing Loss Is Exacerbated by Long-Term Smoking," *Clin. Otolaryngol. 30,* 517–520. doi: 10.1111/j.1749-4486.2005.01105.x.

WorkCover. (2002). *Workcover Guides for the Evaluation of Permanent Impairment,* WorkCover NSW, Canberra, Australia.

Yamane, H., Nakai, Y., Takayama, M., Iguchi, H., Nakagawa, T., and Kojima, A. (1995). "Appearance of Free Radicals in the Guinea Pig Inner Ear after Noise-Induced Acoustic Trauma," *Eur. Arch. Otorhinolaryngol. 252,* 504–508. PMID: 8719596.

Yamashita, D., Jiang, H., Schacht, J., and Miller, J.M. (2004). "Delayed Production of Free Radicals Following Noise Exposure," *Brain Research 1019,* 201–209. doi: 10.1016/j.brainres.2004.05.104.

Yamashita, D., Jiang, H.-Y., Le Prell, C.G., Schacht, J., and Miller, J.M. (2005). "Post-Exposure Treatment Attenuates Noise-Induced Hearing Loss," *Neuroscience 134,* 633–642. doi: 10.1016/j.neuroscience.2005.04.015.

Yang, W.P., Hu, B.H., Chen, G.D., Bielefeld, E.C., and Henderson, D. (2009). "Protective Effect of N-Acetyl-L-Cysteine (L-NAC) against Styrene-Induced Cochlear Injuries," *Acta Otolaryngol. 129,*1036–1043. doi: 10.1080/00016480802566261.

Yeum, K.J., Beretta, G., Krinsky, N.I., Russell, R.M., and Aldini, G. (2009). "Synergistic Interactions of Antioxidant Nutrients in a Biological Model System," *Nutrition 25,* 839–846. doi: 10.1016/j.nut.2009.01.011.

Young, J.S., Upchurch, M.B., Kaufman, M.J., and Fechter, L.D. (1987). "Carbon Monoxide Exposure Potentiates High-Frequency Auditory Threshold Shifts Induced by Noise," *Hear. Res. 26,* 37–43. PMID: 3558142.

Zamyslowska-Szmytke, E., Fuente, A., Niebudek-Bogusz, E., and Sliwinska-Kowalska, M. (2009). "Temporal Processing Disorder Associated with Styrene Exposure," *Audiol. Neurotol. 14,* 296–302. doi: 10.1159/000212108.

Other Resources

Bendich, A., Machlin, L.J., Scandurra, O., Burton, G.W., and Wayner, D.D.M. (1986). "The Antioxidant Role of Vitamin C," *Advances in Free Radical Biology and Medicine 2,* 419–444. doi: 10.1016/s8755-9668(86)80021-7.

Campbell, K.C., Meech, R.P., Rybak, L.P., and Hughes, L.F. (2003). "The Effect of D-Methionine on Cochlear Oxidative State with and without Cisplatin Administration: Mechanisms of Otoprotection," *J. Am. Acad. Audiol. 14,* 144–156. PMID: 12859139.

Carreres Pons, M., Chalansonnet, M., Venet, T., Thomas, A., Nunge, H., Merlen, L., Cosnier, F., Llorens, J., and Campo, P. "Carbon Disulfide Potentiates the Effects of Impulse Noise on the Organ of Corti." *Neurotoxicology 59,* 79–87. doi: 10.1016/j.neuro.2017.02.003.

Clifford, R.E., Coleman, J.K., Balough, B.J., Liu, J., Kopke, R.D., and Jackson, R.L. (2011). "Low-Dose D-Methionine and N-Acetyl-L-Cysteine for Protection from Permanent Noise-Induced Hearing Loss in Chinchillas," *Otolaryngol. Head Neck Surg. 145,* 999–1006. doi: 10.1177/0194599811414496.

Ising, H., Handrock, M., Gunther, T., Fischer, R., and Dombrowski, M. (1982). "Increased Noise Trauma in Guinea Pigs through Magnesium Deficiency," *Arch. Otorhinolaryngol. 236,* 139–146. doi: 10.1007/bf00454034.

Le Prell, C.G., Bledsoe, S.C., Jr., Bobbin, R.P., and Puel. J.L. (2001). "Neurotransmission in the Inner Ear: Functional and Molecular Analyses," in *Physiology of the Ear,* edited by A.F. Jahn and J. Santos-Sacchi, Singular Publishing, New York, NY, 575–611.

Le Prell, C.G., Dolan, D.F., Bennett, D.C., and Boxer, P.A. (2011a). "Nutrient Treatment and Achieved Plasma Levels: Reduction of Noise-Induced Hearing Loss at Multiple Post-Noise Test Times," *Transl. Res. 158,* 54–70. doi: 10.1016/j.trsl.2011.02.003.

Le Prell, C.G., Gagnon, P.M., Bennett, D.C., and Ohlemiller, K.K. (2011b). "Nutrient-Enhanced Diet Reduces Noise-Induced Damage to the Inner Ear and Hearing Loss," *Transl. Res. 158,* 38–53. doi: 10.1016/j.trsl.2011.02.006.

Le Prell, C.G., Dell, S., Hensley, B.N., Hall, J.W.I., Campbell, K.C.M., Antonelli, P.A., Green, G.E., Miller, J.M., and Guire, K. (2012). "Digital Music Exposure Reliably Induces Temporary Threshold Shift (TTS) in Normal Hearing Human Subjects," *Ear Hear. 33,* e44–58. doi: 10.1097/aud.0b013e31825f9d89.

Le Prell, C.G., Ojano-Dirain, C.P., Rudnick, E.W., Nelson, M.A., deRemer, S., Prieskorn, D.M., and Miller, J.M. (2014). "Assessment of Nutrient Supplement to Reduce Gentamicin-Induced Ototoxicity," *J. Assoc. Res. Otolaryngol. 15,* 375–393. doi: 10.1007/s10162-014-0448-x.

Le Prell, C.G., Spankovich, C., White, K., and Lobarinas, E. (2015). "Prevention of Hearing Loss Using Dietary Supplements," *Abs. Assoc. Res. Otolaryngol. 38,* 500.

Lynch, E.D. and Kil, J. (2009). "Development of Ebselen, a Glutathione Peroxidase Mimic, for the Prevention and Treatment of Noise-Induced Hearing Loss," *Semin. Hearing 30,* 47–55. doi: 10.1055/s-0028-1111106.

Lynch, E.D., Kil, J., and Le Prell, C.G. (2016). "Human Clinical Studies in Noise-Induced Hearing Loss," In *Translational Research in Audiology and the Hearing Sciences, Springer Handbook of Auditory Research,* edited by C.G. Le Prell, E. Lobarinas, R.R. Fay, and A.N. Popper, Springer, New York, NY.

Spankovich, C., Hood, L., Silver, H., Lambert, W., Flood, V., and Mitchell, P. (2011). "Associations between Diet and Both High and Low Pure Tone Averages and Transient Evoked Otoacoustic Emissions in an Older Adult Population-Based Study," *J. Am. Acad. Audiol. 22,* 49–58. doi: 10.3766/jaaa.22.1.6.

Tak, J.K. and Park, J.W. (2009). "The Use of Ebselen for Radioprotection in Cultured Cells and Mice," *Free Radic. Biol. Med. 46,* 1177–1185. doi: 10.1016/j.freeradbiomed.2009.01.023.

Wolf, F.I., Maier, J.A., Nasulewicz, A., Feillet-Coudray, C., Simonacci, M., Mazur, A., and Cittadini, A. (2007). "Magnesium and Neoplasia: From Carcinogenesis to Tumor Growth and Progression or Treatment," *Arch. Biochem. Biophys. 458,* 24–32. doi: 10.1016/j.abb.2006.02.016.