Neurotox Res (2016) 30:268–282
DOI 10.1007/s12640-016-9627-3

REVIEW

Ototoxicity of Divalent Metals

Jerome A. Roth[1] · **Richard Salvi**[2]

Received: 16 March 2016 / Revised: 21 April 2016 / Accepted: 22 April 2016 / Published online: 3 May 2016

Abstract Excess exposure to both essential and non-essential heavy metals can lead to a variety of adverse clinical conditions which selectively affect a variety of organs and cells in the body. The diverse, but highly specific nature of the symptoms produced by each metal indicates that they can interact with a restricted population of cellular targets ultimately resulting in unique clinical manifestations. The symptoms, which can be reversible or irreversible, often present with different patterns and outcomes depending on the net accumulated dose of any given metal. There are some common pathological conditions that result from excess exposure to heavy metals which unfortunately have not received widespread recognition and thus, have not been extensively investigated. For example, chronic exposure to several heavy metals such as Co, Mn, Cd, Pb, and Hg has the potential to affect hearing in humans and experimental animals based on previous studies including case reports and ex vivo studies. Understanding exactly how these metals induce hearing deficits is complicated by the fact that the inner ear is an extremely complex system that composed of a diverse collection of sensory, neural, and supporting cells which must act in synchrony to produce a neurophysiological signal terminating in the central auditory system. This review will focus on the anatomical, cellular, and functional changes that occur in the cochlea, the sensory organ for hearing, due to excessive exposure to manganese, cadmium, cobalt, lead, and mercury.

Keywords Metals · Ototoxicity · Hearing loss · Hair cells · Cochlea

Introduction

Excess exposure to both essential and non-essential heavy metals can lead to a variety of adverse clinical conditions which selectively affect different organs and cells in the body. In general, the symptoms are independent of the source of exposure (accidental, environmental, or occupational) but highly dependent on exposure dose and duration which affect the total accumulation of the metal. The highly specific nature of the symptoms suggests that each metal may selectively accumulate in and damage specific cells in the body. Research involving heavy metal toxicity has generally focused on the severe and debilitating disorders affecting major organs such as the heart, lungs, liver, and kidney, while considerably less attention has been given to specialized sensory systems such as the auditory system which plays a critical role in speech and language communication and detecting warning sounds in the environment. Chronic exposure to a number of heavy metals can lead to severe hearing impairment. To appreciate how heavy metals cause hearing loss, it important to understand how they enter the blood stream and then cross the blood–labyrinth barrier (Schmutzhard et al. 2012) to gain access to the sensory hair cells, supporting cells, and auditory neurons in the cochlea, the sensory end organ responsible for converting sound-evoked mechanical vibrations into neural activity that is transmitted to the central auditory system through the auditory nerve (AN). This review will

✉ Jerome A. Roth
jaroth@buffalo.edu

[1] Department of Pharmacology and Toxicology, University at Buffalo, Buffalo, NY 14214, USA

[2] Center for Hearing and Deafness, University at Buffalo, 137 Cary Hall, Buffalo, NY 14214, USA

focus on the ototoxic effects of lead, manganese, cadmium, cobalt, and mercury, heavy metals that damage different structural elements of the cochlea resulting in sensorineural hearing loss.

Anatomy and Function of the Inner Ear

To understand how metals can enter and damage the cochlea and result in hearing loss, it is necessary to briefly review the basic anatomy of the cochlea, which contains the sensory cells responsible for converting sound-induced mechanical vibrations into neural activity. The cochlea is located in a spiral, snail-shaped bony canal located in the temporal bone (Fig. 1a) (Salvi et al. 2009). A cross section taken through bony canal shows the three fluid-filled compartments within, namely scala vestibuli, scala tympani, and scala media (Fig. 1b). These three fluid-filled chambers within the canal spiral around the modiolus, a central bony column; the canal which spirals around the modiolus, extends from the base of the snail-shaped cochlea towards the apex (Fig. 1a). Scala vestibuli and scala tympani are filled with perilymph, a fluid whose ionic composition is similar to cerebrospinal fluid (CSF), i.e., a high concentration of sodium and low concentration of potassium. The fluids within scala tympani and scala vestibuli are connected to one another through the helicotrema, a small opening located near the apex of the cochlea (Fig. 1a). Scala media, which lies between scala vestibuli and scala tympani is bounded by Reissner's membrane and the reticular lamina, the upper surface of the organ of Corti which rests on the basilar membrane. Scala media is filled with endolymph, which has a high concentration of potassium and a low concentration of sodium, similar to intracellular fluid. Importantly, the electrical potential of the endolymph is +80 mV providing an electromotive force that helps to drive the positively charged potassium ions in the endolymph into the hair cells which have a resting potential of approximately −60 mV; this results in roughly a 140 mV gradient across the apical pole of the hair cells.

The sensory epithelium comprised sensory hair cells and a variety of supporting cells forms the organ of Corti which rests on the basilar membrane (Fig. 1b, c). The basilar membrane stretches medially from a bony ledge on the modiolus outward towards the spiral limbus located on the lateral bony wall of the cochlea. Within the canal, the basilar membrane spirals around the modiolus from the base to apex. Sounds impinging on the tympanic membrane (ear drum) are transmitted through the three middle ear ossicles, the malleus, incus, and stapes (Fig. 1a). The footplate of the stapes attaches via a flexible ligament into the oval window in scala vestibuli. The inward and outward motion of the stapes causes a pressure disturbance that propagates almost instantaneously through the fluids causing the basilar membrane to vibrate. Due to the mass and stiffness gradient along the length of the basilar membrane, the incoming sounds are spectrally filtered such that high-frequency sounds induce maximum displacement of the basilar membrane near the base of the cochlea. As frequency decreases, the point of maximum displacement shifts from the base toward the apex setting up a tonotopic gradient reminiscent of a piano keyboard. The spectrally filtered vibrations of the basilar membrane stimulate the sensory hair cells located on the basilar membrane. Three parallel rows of outer hair cells (OHCs) and one row of inner hair cells (IHCs) are located on the basilar membrane of the organ of Corti (Fig. 1b, c). The IHCs are located medial to the inner pillar cells near the modiolus while the OHCs lie lateral to the outer pillar cells closer to the lateral wall of the cochlea. The inner and outer pillar cells form the arch of Corti which lies between the IHCs and OHCs. Projecting from the apical surface of each hair cells is a stereocilia bundle; the stereocilia are graded in height forming a staircase with the shortest row of stereocilia located nearest to the modiolus and the tallest row located more laterally. Deflection of the stereocilia bundle in the direction of the tallest row of stereocilia results in depolarization and excitation of the hair cells.

The hair cells in the organ of Corti are innervated by roughly 50,000 spiral ganglion neurons (SGN). The cell bodies of the SGN neurons lie within the central core of the modiolus. As implied by its name, the cell bodies of the SGN spirals around the modiolus from base to apex. Approximately 90–95 % of SGN are classified as type I; the remaining 5–10 % are classified as type II (Fig. 1d). The peripheral processes of the type I neurons extend out radially and make contact with a single IHC; roughly 10–20 type I neurons innervate a single IHC. In contrast, the peripheral processes of the type II neurons extend out radially crossing the tunnel of Corti and then spiral basalward several millimeters contacting multiple OHC. The axons of type I and type II neurons form a bundle within the central core of the modiolus that extends medial to form a bundle that becomes the AN portion of the 8th cranial nerve that project into the cochlear nucleus (CN) in the brainstem (Fig. 1d).

The lateral wall of the cochlea contains the stria vascularis, a highly vascularized tissue that forms the blood–cochlear barrier (Qi et al. 2014). The marginal, intermediate, and basal cell layers of the stria vascularis, adjacent to the endolymph contains numerous pumps and ion channels that regulate the flow of fluids and ions into and out of the endolymph. The toxic effects of various heavy metals on the cochlea are critically dependent on the blood–cochlear barrier, ion channels, and transporters

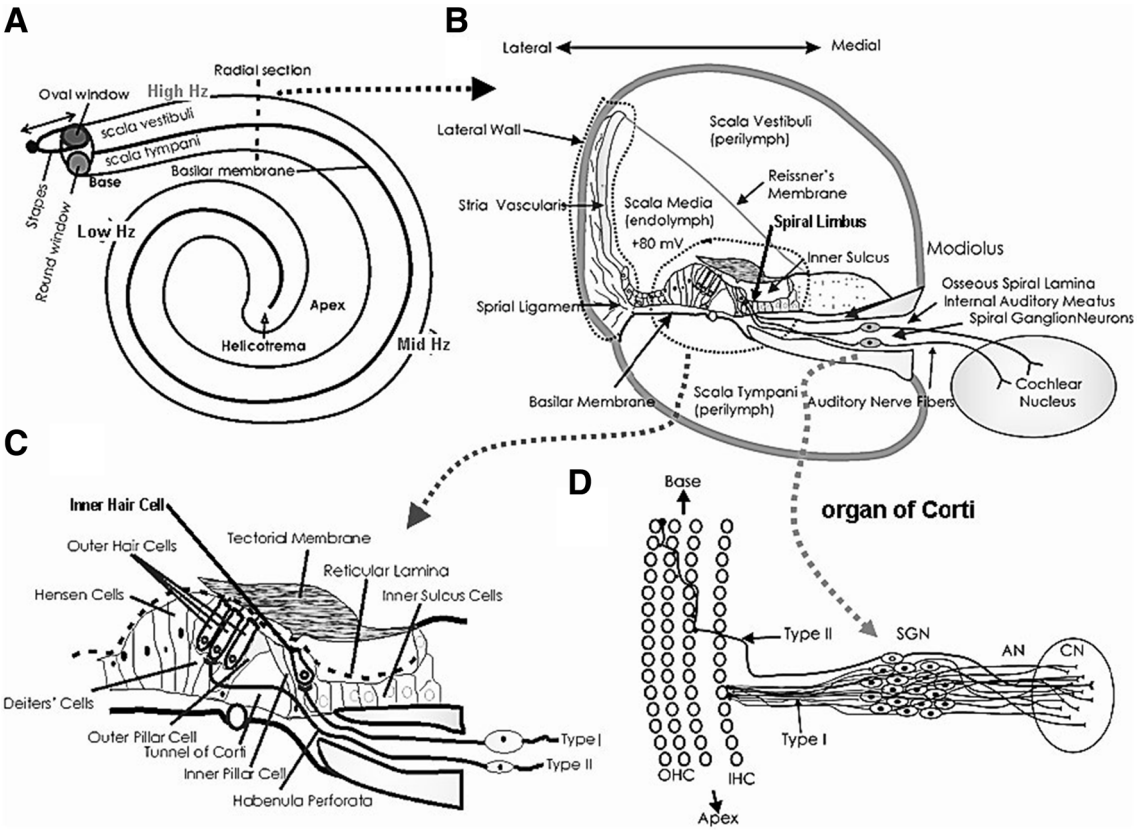

Fig. 1 Schematic of the cochlea. **a** External view of the spiral-shaped cochlea; cochlea partially unwound to its overall organization. The stapes of the middle ear ossicles inserts into the oval widow which faces the fluids in scala vestibuli. The fluids in perilymph communicate with those in the scala tympani through the helicotrema, a small opening at the apical end of scala vestibuli. Low-frequency sounds produce maximum vibration in the apex of the cochlea, mid-frequency sounds produce maximum vibration in the middle of the cochlea, and high-frequency sounds produce maximum vibration in the base. Radial section (*dashed line*) through the cochlea shows the fluid-filled compartments and structures within each cochlear turn. **b** Radial cross section showing key structures in the lateral wall (stria vascularis and spiral ligament), the three fluid-filled compartments (scala vestibuli, scala media, and scala tympani), Reissner's membrane, the organ of Corti (*dashed circle*) resting on the basilar membrane, the inner sulcus region, the osseous spiral lamina containing the spiral ganglion neurons, the AN fibers exiting the cochlea and terminating in the cochlear nucleus in the brainstem. **c** Expanded view of the organ of Corti showing the outer hair cells, inner hair cells, tunnel of Corti, inner pillar cells, outer pillar cells, Deiters' cells, Hensen cells, type I and type II nerve fibers passing through the habenula perforata on their way to the hair cells. *Dashed line* shows the reticular lamina, a series of tight cell junctions that form the fluid boundary separating scala medial from scala tympani. **d** Surface view of the organ of Corti showing the three parallel rows of outer hair cells and single row of inner hair cells extending from the base toward the apex. The spiral ganglion neurons (SGN) are composed of type I (90–95 %) and type II (5–10 %) neurons. The peripheral process of each spiral ganglion neurons extends out radially to contact the hair cells while the central process projects medially to form the AN. The AN fibers terminate in the cochlear nucleus (CN) in the brainstem. The peripheral process of each type I neurons contact a single inner hair cell; approximately 10–20 type I fibers contact a single inner hair cell. The peripheral process of type II neurons project out radially, crosses the organ of Corti, and then turns and runs towards the base of the cochlea for a few mm making synaptic contact with multiple outer hair cells

located in the stria vascularis; these structures tightly regulate the flow of metal ions from the blood into the fluid spaces within the cochlea. After entering the fluid spaces within the cochlea, each heavy metal must be actively or passively transported from the extracellular space through the cell's plasma membrane and into the cytoplasm or intracellular organelles.

The following sections describe some of toxic effects of several widely used heavy metals, their main source of contamination in the environment, and their deleterious effects on the structure and function of the cochlea and hearing.

Cadmium (Cd)

Cadmium (Cd), a non-essential heavy metal, is widely used in the production of batteries, solar panels, pigments, and plastic stabilizers (Banci et al. 2006; Basinger et al. 1987; Herber 1992; Huff et al. 2007). Cd typically enters the

body from contaminated food and water as well as through inhalation of polluted air and cigarette smoke. Environmental pollution of Cd typically results from excessive industrial emissions during the smelting and refining of metals as well as in the production of batteries, alloys, and pigments. Of the 189 hazardous air pollutants in the Environmental Protection Agency (EPA) National Emission Standards for Hazardous Air Pollutants (NESHAP), Cd is ranked number 33 in terms of threat to public health in urban areas. Interestingly, chronic exposure to Cd results in protracted accumulation in the body as the biological half-life is estimated to be between 6 and 38 years (U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry).

The normal daily intake of Cd through food varies greatly in different regions. Daily consumption varies between 8 and 30 μg though in some highly contaminated areas intake can be substantially greater. Over exposure has been linked to a wide range of adverse medical conditions including cancer, nephrotoxicity, bone disease, and hepatotoxicity. Humans as well as laboratory animals can also develop a severe and irreversible neurological disorder due to excess intake of Cd. Cd-induced neurotoxicity affects both the central and peripheral nervous system in humans, with greatest neurotoxicity occurring in the developing brain (Antonini 2003; Rigon et al. 2008; Viaene et al., 1999, 2000). The American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) for Cd dust and salts is 50 $\mu g/m^3$ for an 8-h time-weighted average, with a 15-min short-term exposure limit of 200 $\mu g/m^3$.

The components controlling Cd toxicity are the rate of cellular uptake, exposure duration, and overall accumulation which directly and indirectly impacts biochemical reactions within cells. Absorption of Cd is affected by iron and other divalent metals, as these metals share common transmembrane transport proteins such as divalent metal transporter 1 (DMT1), ZIP8 and ZIP14 (Garrick et al. 2006; Illing et al. 2012; Pinilla-Tenas et al. 2011; Wang et al. 2012). DMT1 is composed of four distinct isoforms which differ in their C and N terminals all of which are transcribed from a common gene (Garrick et al. 2012; Roth 2006). The four isoforms differ in their cellular and subcellular location but essentially have the same affinities for the different divalent metals. Both ZIP8 and 14 are divalent cation/HCO_3^- symporters with the transmembrane HCO_3^- gradient acting as the driving force for divalent metal transport. Both are members of the solute carrier families 39 (SLC39) which are capable of transporting a variety of endogenous and exogenous divalent cations. All three transporters are present within different cells of the cochlea (Ding et al. 2014a, b).

Mechanism of Cd Toxicity

The mechanisms of Cd-induced toxicity are not fully understood due to the fact that Cd can influence a multitude of cellular processes including cell proliferation and differentiation, cell cycle progression, DNA synthesis and methylation, ubiquitination, apoptosis, and other cellular activities all of which potentially can lead to cell death (Aimola et al. 2012). Therefore, the mechanisms responsible for Cd toxicity are likely multifaceted and may vary within different cells and organelles. Upon absorption into the body, Cd is capable of displacing several different protein-bound essential divalent metals including Zn, Fe, Mg, Mn, Ca, and Se (Sarkar et al. 2015) by interfering with covalent and ionic bonds to sulfur, oxygen, and hydrogen, This likely promotes significant disruption of protein activity required for homeostasis (Bertin and Averbeck 2006). Therefore, Cd toxicity may be caused by differences in specific protein binding sites created by developmental or epigenetic variation in the intracellular composition of cells and interfere with a diverse array of cell signaling pathways thereby influencing the activity of receptors, second messengers, and transcription factors.

The main target organelle of Cd is thought to be mitochondria (Choong et al. 2014; Koizumi et al. 1996). Cd can enter mitochondria through calcium channels resulting in structural changes in membrane proteins via binding to thiol groups which impedes oxidative phosphorylation and ATP production as well as disrupting the permeability transition pore with the eventual leakage of cytochrome c. The net effect is decreased energy for maintenance of cellular function and increased production of reactive oxygen species (ROS) followed by the ensuing oxidative stress promoting activation of various downstream signals related to apoptotic cell death. Although the general consensus is that Cd-induced cell death is typically mediated by apoptosis, necrosis has also been proposed (Prozialeck et al. 2009). Necrosis, can also induce an inflammatory response that exacerbates oxidative stress (Messner et al. 2015). Cd may also promote autophagy (Wang et al. 2008) which allows for the digestion of dysfunctional organelles within lysosomal–autophagic vacuoles.

Cd Ototoxicity

Although research on the ototoxic effects of Cd is sparse, there is substantive evidence demonstrating that Cd can damage the cochlea leading to significant hearing loss (Agirdir et al. 2002; Kim et al. 2008, 2009). There is, however, a lack of information regarding the mechanism by which Cd induces hearing loss and the specific anatomical structures which are damaged. Several studies have suggested that cellular elements within the inner ear

behave much like the kidney given the fact that many drugs that are nephrotoxic are also ototoxic (Humes 1999). This is important as the highest concentrations of Cd are observed in the kidney, which is considered to be one of the major organs for Cd-related toxicities (Hamada et al. 1997; Nogawa et al. 1983). Indeed, Cd accumulates in the cochlea when rats are treated for 30 days with $CdCl_2$ (15 ppm) in drinking water; the animals not only display significant nephrotoxicity but hearing loss as well (Ozcaglar et al. 2001). Cd treatment leads to a reduction in otoacoustic emissions, indicative of damage to OHC and/or the stria vascularis (Ozcaglar et al. 2001). The latency of wave I of the auditory brainstem response (ABR), which originates from the AN, was also greatly delayed, suggesting possible damage to the SGN as well. Surprisingly, the latencies of waves III and V, which emanate from the auditory brainstem, did not change significantly, suggesting that the cochlea is more vulnerable to the toxic effects of Cd than neurons in the auditory brainstem though direct evidence for this is lacking.

In another study, Cd toxicity was assessed in explants of the organ of Corti as well as an organ of Corti-derived cell line, HEI-OC1, which shares characteristics of hair cell progenitors (Kim et al. 2009). Cd exposure caused cell death, ROS generation, matrix metalloproteinase loss, release of cytochrome c, activation of caspases and ERK, and apoptotic cell death. Cd also interfered with inhibitors of cell signaling pathways, including ERK and c-jun N-terminal kinase. The antioxidants *N*-acetyl-L-cysteine and ebselen conferred significant protection against Cd ototoxicity implying that cell death was likely caused by oxidative stress. In addition, rats exposed to high doses (150 ppm) of Cd for 30 days in drinking developed an ABR threshold shift at 32 kHz which was partially prevented by the antioxidant, *N*-acetylcysteine further suggesting that oxidative stress is involved in Cd toxicity.

Using postnatal cochlear organotypic cultures, our laboratory demonstrated Cd-induced damage to hair cells, AN fibers and SGN; the damage was dose and duration dependent (Liu et al. 2014). Exposure to Cd concentrations as low as 10 μM for 24 and 48 h resulted in IHC and OHC loss in the basal third of the cochlea. Treatment with 100 μM Cd for 48 h resulted in substantial hair cell loss over the entire cochlea as well as extensive damage to AN fibers and SGN. Hair cell loss began at the base of the cochlea and progressed towards the apex with increased dose and duration of treatment similar to other ototoxic drugs and toxic reagents (Ding et al. 2007, 2011; Ding and Gong 2004; Li et al. 2011; Qi et al. 2008). These in vitro data are remarkably consistent with cochlear hair cell loss in animal models (Agirdir et al. 2002; Ozcaglar et al. 2001; Prasher 2009; Whitworth et al. 1999). Mechanistically, Cd-induced degenerations in hair cells and SGNs was associated with TUNEL staining and nuclear condensation and fragmentation indicative of cell death mediated by apoptosis (Chabicovsky et al. 2004; Chao and Yang 2001; Chatterjee et al. 2009; Coutant et al. 2006; Lasfer et al. 2008; Xu et al. 1996).

Manganese (Mn)

Mn was recognized over 85 years ago as an essential nutrient necessary for regulating reproduction, formation of connective tissue and bone, carbohydrate and lipid metabolism, and brain function (Bourre 2006; Keen et al. 1999; Kemmerer et al. 1931; Orent and McCollum 1931). Because of the abundant supply in our normal diet, Mn deficiency in adults is essentially nonexistent though deficiency during fetal development results in neurological and behavioral deficits as well as abnormal growth of a variety of systems (Hurley 1981; Strause et al. 1986). In contrast, overexposure to Mn produces a severe and debilitating disorder known as manganism (Krieger et al. 1995; Pomier-Layrargues et al. 1995). The most prominent, irreversible symptom associated with chronic Mn exposure is a distinct extra-pyramidal syndrome which partially resembles the dystonic movements associated with Parkinson's disease (Huang et al. 1993; Olanow et al. 1996; Pal et al. 1999). Manganism is most often seen in individuals with protracted exposure to high atmospheric levels of Mn such as welders, Mn miners, and ferroalloy workers. The permissible exposure level (PEL) for Mn fume levels established by Occupational Safety and Health Administration (OSHA) is 5 mg/m^3 and the TLV is 0.2 mg Mn/m^3 for elemental Mn whereas the National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL) is 1 mg/m^3 (U.S. Department of Labor; OSHA). Acceptable levels in drinking water are set at 0.05 mg/l. Individuals with chronic hepatic failure also display elevated serum and brain levels of Mn and exhibit many of the behavioral deficits and neurodegenerative features observed in occupationally exposed workers primarily because the liver is the major organ responsible for its elimination from the body (Burkhard et al. 2003; Hauser and Zesiewicz 1996; Hauser et al. 1994; Krieger et al. 1995; Pomier-Layrargues et al. 1995).

The classical symptoms of manganism were initially describes almost 180 years ago by Couper (Couper 1837; Lucchini et al. 2009; Santamaria and Sulsky 2010) in men using a grinding wheel composed of the black oxides of manganese. Although sporadic reports of Mn toxicity appeared in the literature in the early 1990s, its definitive association with the metal has only been acknowledged in the last several decades as a result of significant progress in understanding its cytotoxicity.

Because of the severe and irreversible consequences of Mn overexposure to the CNS, most research has focused on the critical mechanisms leading to manganism. Less well recognized is that chronic exposure to Mn also has harmful consequences to other organs such as the respiratory and auditory systems. For example, chronic exposure to Mn can lead to increased propensity to develop pulmonary infections including pneumonia and bronchitis (Antonini et al. 2009; Bencko and Cikrt 1984; Bowler et al. 2007; Saric and Piasek 2000). Welding fumes with the highest content of Mn were also reported to have the greatest propensity to cause lung inflammation, injury, and to produce inflammatory cytokines and chemokines (Antonini et al. 2012).

Mechanism of Mn Toxicity

Considerable progress has been made in the past few decades in understanding Mn-induced cell death. Both apoptosis and necrosis have been implicated in Mn-induced cell degeneration. Mn has been shown to activate many of the signaling pathways associated with programed cell death as reflected in elevated TUNEL staining, internucleosomal DNA cleavage, cytochrome c release, and activation of the JNK, p38 kinase, and caspase pathways (Chun et al. 2001; Desole et al. 1997; Hirata et al. 1998; Kitazawa et al. 2005; Roth 2006; Roth et al. 2000; Schrantz et al. 1999). Loss of mitochondrial function results in the production of ROS triggering an oxidative stress-signaling cascade leading to apoptotic cell death. Mn, which is taken up into mitochondria via the Ca^{2+} uniporter, induces mitochondrial membrane transients promoting disruption of mitochondrial function (Gavin et al. 1990, 1999; Martinez-Finley et al. 2013). Opening of the mitochondrial permeability transition pore (PTP) caused by increased levels of Ca^{2+} in the mitochondria due to Mn inhibition of the sodium-dependent and sodium-independent Ca^{2+} exporter. Mn also interferes with oxidative phosphorylation by inhibiting mitochondrial F1-ATPase and complex I, causing a depletion of ATP (Chen and Liao 2002; Roth et al. 2000, 2002). Loss of ATP is consistent with necrosis-induced cell death.

Similar to several other divalent heavy metals such as Fe, Cd, and Co, Mn is transported into cells via DMT1, ZIP8, and ZIP14 (Roth et al. 2013). All three carrier-mediated transporters have a relatively high affinity for Mn. Mn is also taken up into cells by the voltage-gated Ca channels (Anderson 1983) as well as ionotropic glutamate channels (Kannurpatti et al. 2000). Although DMT1 has generally been accepted as the major membrane carrier of Mn, there is increasing evidence that the ZIP proteins play a significant role as well (Ding et al. 2014b; Fujishiro et al. 2012; Jenkitkasemwong et al. 2012). The zinc membrane carrier, SLC30A10, has recently been identified as the major exporter of Mn and mutations in this gene lead to Mn accumulation and the characteristic symptoms of manganism (Quadri et al. 2012; Tuschl et al. 2012).

Mn Ototoxicity

Several case reports in the literature suggest that Mn may cause or contribute to hearing loss in workers chronically exposed to high levels of the metal (Bouchard et al. 2008; Da Silva et al. 2007; Josephs et al. 2005; Khalkova and Kostadinova 1986; Korczynski 2000; Nikolov 1974; Park et al. 2006). Hearing deficits have been reported in welders chronically exposed to fumes with high levels of Mn and in workers exposed to noise and Mn. Unfortunately, these clinical findings are limited and largely inconclusive to the role of Mn due multiple confounding factor such as noise, aging, and smoking. Recent laboratory studies have shown that Mn accumulates in the inner ear of rats (Ma et al. 2008) raising the possibility that it may damage hair cells, neurons, or supporting cells in the cochlea. In studies using cochlear organotypic cultures from postnatal day 3 rats, Mn damaged cochlear hair cells, AN fibers, and SGN in a dose- and duration-dependent manner with the nerve fibers being most vulnerable (Ding et al. 2011). Surprisingly, IHC were more sensitive than OHC to Mn damage. Based on these in vitro findings, it is possible that excess exposure to Mn has the potential to induce hearing loss in humans and experimental animals.

Cobalt (Co)

Co, a required divalent metal ubiquitously expressed in the environment, is used extensively in the production of batteries, metal alloys, and blue pigment. Co being part of the vitamin B12 complex is essential for human health because it plays a key role in the formation of red blood cells, synthesis of DNA and regulation of fatty acid and amino acid metabolism (Yamada 2013). The Center for Food Safety and Applied Nutrition recommends a daily intake of Co, as vitamin B12, of 6 μg per day for adults and children 4 years or older although, normal daily intake often exceeds this amount. Gastrointestinal absorption is relatively low, varying from 5 to 45 % depending on the solubility of the Co species ingested. Absorption is affected by iron and other divalent metals as these metals share common transmembrane proteins including DMT1, ZIP8, and Zip14. Since Co is also transported into cells through glutamate receptors (Malva et al. 2003), it is conceivable that these receptors contribute to Co-induced neurotoxicity in the brain or cochlea (Kuriyama et al. 1994; Ruel et al. 1999).

The concentration of free-ionized Co in serum is functionally distinct from that of Co present within the corrin ring of Vitamin B12, as the ingested divalent species cannot be incorporated into cobalamin. The majority of the ionized Co in plasma is bound to serum albumin and other serum proteins, but approximately 5–12 % of the total is in its free fraction which can readily be eliminated in urine (Simonsen et al. 2012). The divalent species of Co accumulates primarily in the liver, kidney, pancreas, and heart, with increasing amounts accumulating over time in skeleton and skeletal muscles. The half-life of Co in the body ranges from approximately 5 days to 4 years depending on the compound, route of exposure, and biochemical composition within any organ (OSHA).

More than a million US workers are exposed to excess Co with the greatest exposure occurring in mining, production of Co powder, tungsten carbide, other alloys, and manufacturing and processing of hard metals. Excess exposure to Co can lead to severe sensory disturbances including hearing loss (Apostoli et al. 2013; Bradberry et al. 2014; Ikeda et al. 2010). The Department of Defense compared $CoCl_2$ toxicity to other known toxins and identified it as potentially the most toxic chemical among other substances in a class of 36 pure elements and metals used in industrial applications (Permenter et al. 2013; Sutto 2011). The lethal dose, 50 % (LD50) value, for soluble Co salts in rats has been estimated to be between 150 and 500 mg/kg (Donaldson and Beyersmann 2005). Humans are typically exposed to Co through air and diet, but in some cases dermatological exposure occurs through soil or water. Acute and chronic exposure to high levels of Co by inhalation in industrial settings can result in respiratory dysfunction caused by congestion and edema along with increases in asthma, pneumonia, and fibrosis (Rehfisch et al. 2012; Simonsen et al. 2012; Swennen et al. 1993). Additional deleterious consequences from chronic exposure also include impaired functioning of heart, liver, kidney, conjunctiva, thyroid, immune system, vision, and hearing. One notable toxic consequence of Co overexposure is a severe and often lethal cardiomyopathy (Seghizzi et al. 1994). There is also evidence that Co may increase the risk of pheochromocytomas, adrenal gland tumors, and other cancers, however, the EPA has not classified it as a cancer-inducing agent.

Mechanism of Co Toxicity

The mechanisms by which Co induces cell loss is not fully understood but likely is initiated by mitochondrial dysfunction. The divalent species of Co has been reported to induce the formation of ROS and alters the mitochondrial permeability transition pore leading to mitochondrial swelling and electrical membrane potential collapse (Battaglia et al. 2009). Co also acts as a putative inhibitor of Ca channels and Ca signaling as well as competing with Ca for intracellular Ca-binding proteins (Simonsen et al. 2011, 2012). One of the most critical actions of both the monovalent and divalent forms of Co is in its role in supporting the Fenton's reaction resulting from the production of hydrogen peroxide that is converted to the highly toxic hydroxyl radical (Leonard et al. 1998; Scharf et al. 2014). Excess intracellular Co leads to the release of cytochrome c and activation of caspase and MAPK (Kim et al. 2003; Petit et al. 2004) all of which promote apoptosis. Co is also a hypoxia-mimetic agent capable of switching cell metabolism from aerobic respiration to anaerobic glycolysis leading to the production of HIF-1α expression (Karovic et al. 2007). HIFα is critical to the action of Co as it can have opposing effects inducing both pro-apoptotic and anti-apoptotic signaling pathways. Co can also decrease the expression of extracellular superoxide dismutase which scavenges the highly toxic superoxide anion leading to the activation of caspase-3 and DNA fragmentation (Adachi et al. 2011). In addition, Co intoxication can activate a stress response program, proteasome activity, and a NF-kB mediated proinflammatory response supporting necrotic cell death (Rovetta et al. 2013).

Co Ototoxicity

Several case reports have suggested that excess exposure to Co from metal implants or occupational inhalation can cause severe hearing loss in univariate analyses (Bradberry et al. 2014; Ikeda et al. 2010; Pizon et al. 2013). This was highlighted by the observation that patients with malfunctioning hip implants had serum Co concentrations up to 100-fold greater than normal with almost all subjects displaying severe hearing loss (Oldenburg et al. 2009; Pelclova et al. 2012; Pizon et al. 2013). Interestingly, removal of the Co-containing implant in some cases resulted in partial recovery of some of the neurological symptoms with the exception of hearing loss which persisted over the time of the study (Pelclova et al. 2012). Hearing impairment induced by Co is also a prominent feature often seen in occupations where exposure is a daily occurrence (Paustenbach et al. 2013).

There is a paucity of animal studies of Co-induced ototoxicity which could help clarify our understanding of the physiological and biochemical basis for the hearing deficits seen in humans. One recent histological study of rabbits given high intravenous injections of Co for up to 18 days suggested that Co was capable of inducing degeneration of both the IHC and OHC however, its effect on the stria vascularis, an important site of drug entry into the cochlea was not described (Apostoli et al. 2013). Since there was no functional assessment of hearing in the

rabbits, it is unclear how much hearing loss Co induced and what frequencies were affected.

Although hearing loss has been reported in individuals exposed to excess Co, the exact nature of the histopathologies and mechanisms responsible for cell death within the cochlea is poorly understood. Although some studies have suggested that Co preferentially damages the sensory hair cells, more recent studies in our laboratory (Li et al. 2015) using an in vitro cochlear culture model suggest that SGN may be equally or slightly more sensitive than hair cells to the toxic actions of Co. It is important to note that if Co preferentially damaged SGN, the ensuing damage might go undetected by the conventionally pure tone audiogram which is insensitive to the damage to SGN and type I AN fibers (Lobarinas et al. 2013). In this case, selective damage to SGN or IHC results in "hidden hearing loss" with the functional hearing impairment only detectable by measuring the compound action potential (CAP) or wave I of the ABR.

Lead (Pb)

Pb exposure continues to be a major public health problem particularly in urban areas in the US and in developing nations. OSHA estimates that approximately 804,000 workers in general industry and an additional 838,000 workers in construction are potentially exposed to noxious levels of Pb. Of all the heavy metals, Pb is probably one of the most recognized toxic agents known to the general public because of the adverse publicity it has received concerning its detrimental health effects in children. Pb ranks second among 275 chemicals on the ATSDR/EPA Priority List of Hazardous Substances. Pb causes a wide range of neurotoxic effects in both adults and children, including cognitive dysfunction (Counter et al. 2009a, b; Huang et al. 2012; Mason et al. 2014; Weisskopf et al. 2007), oxidative stress (Lopes et al. 2016), and disruption of the permeability barrier of brain (Shi and Zheng 2007). Prior studies have indicated that Pb exposure is a high risk factor to the auditory system (Counter and Buchanan 2002; Dietrich et al. 1992; Jones et al. 2008; Osman et al. 1999; Otto and Fox 1993; Staudinger and Roth 1998; Yamamura et al. 1989).

Recognition of these health risks has, appropriately, brought about its reduction in use not only as a paint pigment and as an additive in gasoline (Needleman 2000) but also in industrial products such as solder and pipes. Although Pb salts are often present in small concentrations in food, water, and air; such exposures exceed the EPA maximum contaminant-level goal (MLCG) of 0 indicative of the highly toxic nature of this metal. In the workplace, the established permissible exposure limit (PEL) is 50 $\mu g/m^3$ of Pb over an 8-h time-weighted average though levels of 30 $\mu g/m^3$ requires employers to begin specific compliance activities (OSHA). Adverse health effects produced by Pb exposure include intellectual and behavioral deficits in children, including hyperactivity as well as deficits in fine motor control, hand-eye coordination, and reaction time (Sanders et al. 2009). Recent findings revealed other adverse effects such as hypertension and cardiovascular and renal diseases (Vaziri and Gonick 2008). Chronic Pb exposure in adults can also promote decreased fertility (Sallmen 2001), cataracts (Schaumberg et al. 2004), nerve disorders, muscle and joint pain, and memory and concentration problems. Extreme exposure to Pb can provoke convulsions and even coma. Most importantly, Pb has been recognized as a developmental neurotoxicant that can affect the developing fetal brain leading to its functional impairment. The inability of the humans to eliminate Pb efficiently results in its accumulation in the body. The half-life of Pb in blood is around 28–36 days but almost 2 years in brain whereas in bone it can persist for decades (Lidsky and Schneider 2003).

Mechanism of Pb Toxicity

Although the clinical manifestations from overexposure to Pb have been exhaustively studied, the precise mechanism for its toxic actions is not well understood. The reason for the ambiguity partially stems from the fact that Pb can bind indiscriminately to sulfhydryl groups and can adversely mimic protein binding of several different required metals with the net effect of influencing a variety of homeostatic systems within cells (Lopes et al. 2016). Similar to other heavy metals, toxicity is multifaceted, dose dependent, and contingent on the unique structural and biochemical composition of the cell. Also similar to other divalent metals, lead is transported by DMT1 (Bressler et al. 2004; Wang et al. 2011).

The influence of Pb on mitochondrial activity has been proposed to be a major mechanism leading to cell demise, similar to several other divalent cations (Sousa and Soares 2014; Watrach 1964). Pb can inhibit mitochondrial calcium uptake and potentiate calcium release, both of which results in the opening of the mitochondrial permeability transition pore causing release of cytochrome c. The ensuing oxidative stress arises from two different pathways which include increased generation of ROS (Hsu et al. 1997) as well as the additive effect of reduction of antioxidant reserves (Ahamed and Siddiqui 2007) which promote apoptosis. The reduction of antioxidant reserves is significant as the antioxidant defenses largely quench the deleterious actions of free radicals preventing much of the oxidative stress imposed on the degenerating cell. One of the most important antioxidants found in cells is reduced

glutathione. Pb binding to the sulfhydryl group in reduced glutathione results in its inactivation which abolishes its antioxidant activity. Pb is also capable of inactivating glutathione reductase, glutathione peroxidase, and glutathione S-transferase all which further reduce glutathione levels (Ahamed and Siddiqui 2007). Other prominent antioxidant enzymes which are inactivated by Pb include superoxide dismutase and catalase (Agrawal et al. 2014). In addition, Pb can also replace the Zn and Ca ions that function as important co-factors for these antioxidant enzymes and further promote their inactivation (Flora 2002; Garza et al. 2006; Pande and Flora 2002).

Pb Ototoxicity

Pb is toxic to nearly all organs of the body; therefore, it is not surprising that hearing deficits have been reported due to excess Pb exposure. Although the literature describing Pb ototoxicity is limited, the data clearly establishes that blood levels of Pb directly correlate with hearing loss in humans and laboratory animals. A comprehensive study (Schwartz and Otto 1987) using over 4000 subjects aged 4–19 indicated a high correlation between blood levels of Pb and elevated hearing threshold at 500, 1000, 2000, 4000 Hz using NHANES II audiometry data. In a laboratory study in which $PbAC_2$ was administrated daily to rats for 8 weeks at a dose of 300 ppm and to guinea pigs at a dose of 50 mg/kg twice a week for 8 weeks, ABR hearing threshold increased substantially in both rats and guinea pigs. Hearing impairment was correlated with the loss of OHC (Liu et al. 2013). Pb also disrupted the tight junctions between the endothelial cells and the border cells suggesting that Pb may increase the permeability of the blood–cochlea barrier allowing other toxicants to invade the inner ear, and thereby further contribute to the impairment of auditory function. Other results (Liu et al. 2011) show that Pb did not alter the interpeak latencies of waves I–III, III–V, and I–V, indicating that Pb-induced hearing loss is mainly due to cochlear damage rather demyelination of the auditory brainstem.

To determine whether Pb can directly affect the components of the cochlea, in vitro studies were performed in which postnatal rat cochlear organotypic cultures were treated for 24 and 72 h with various doses of Pb acetate (Xue-wen et al. 2011). Little damage was noted at 24 h at any of the doses used; however, treatment for 72 h with high Pb concentrations exceeding 2 mM resulted in severe damage to the peripheral AN fibers and SGN. Many SGNs appeared condensed or shrunken and displayed positive TUNEL staining indicative of apoptotic cell death. These results support the prior investigation suggesting that Pb primarily damages cochlear nerve fibers and SGN as opposed to hair cells.

In summary, these findings support the model whereby Pb can directly cause hearing loss by damaging the cochlea with the majority of the studies indicating that neurons in the cochlea are more sensitive than hair cells to Pb damage suggesting that these cells may be the major target responsible for the hearing deficits observed.

Mercury (Hg)

Hg occurs in a variety of physical and chemical states which influence its toxic actions. The principal species in the earth's atmosphere is a monatomic gaseous vapor which is stable at room temperatures. It is estimated that approximately half the total Hg present in the atmosphere correlates with a variety of industrial applications such as burning of fossil fuels, smelting metal ores, mercury mining, and waste incinerators (Clarkson 1993; Rice et al. 2014; Syversen and Kaur 2012). Hg in the atmosphere is normally converted to water-soluble species, presumably by oxidation to divalent inorganic Hg^{2+}, which is deposited back to the earth's surface in rain water. It is important to recognize that Hg which also settles in the sediment of rivers and lakes readily undergoes methylation by microorganisms. Both Hg and its organic derivatives, such as dimethylmercury and methylmercury, are extremely toxic with the organic forms being particularly hazardous because of their increased lipid solubility facilitating their absorption through the skin and mucous membranes.

In the past, Hg compounds in the environment primarily resulted from their use in fungicides or as byproducts of Hg salts in the chemical industry. Because of its publicized toxicity, Hg exposure from industrial application has decrease considerably over the past several decades. The principal source now appears to be the organic species of Hg which has bioaccumulated in marine sediments ultimately entering the aquatic food chain in edible tissues of fish living in both fresh and ocean waters.

The organic forms of Hg being highly lipid soluble are readily taken up in the intestines and cross the blood–brain barrier where its principal neurological effects are seen. In contrast, the divalent species is transported like other heavy metals by DMT1 (Vazquez et al. 2015). The biological half-life of methylmercury in humans is around 50 days and it is mainly eliminated in the feces as inorganic Hg. Once absorbed into blood, mercury enters erythrocytes where the majority is bound to form a ternary mixed ligand complex between glutathione (GSH)–Hg^{2+}–hemoglobin whereas lesser amounts are attached to other plasma proteins (Rabenstein and Isab 1982). Approximately 10 % of the body burden of methylmercury is presumed to be associated with brain where it readily undergoes demethylation to inorganic Hg. Toxic manifestations

include damage to specific anatomical sites within the brain such as the visual cortex and granule layer of the cerebellum though these lesions may necessitate extended time to appear. Symptoms may include paresthesia, ataxia, constriction of the visual fields, and hearing loss.

OSHA has set the legal airborne Hg permissible exposure limit (PEL) at 0.1 mg/m^3; the NIOSH recommended airborne exposure limit (REL) is 0.05 mg/m^3 as Hg vapor averaged over an 8-h workday and 0.1 mg/m^3 which is not to be exceeded at any time. American Conference of Governmental Industrial Hygienists (ACGIH) has set the TLV as 0.025 mg/m^3 averaged over an 8-h workday while EPA has set a limit of 2 parts of mercury per billion parts of drinking water. Inhaling $HgCl_2$ has been reported to cause irritation to the respiratory system including nose, throat, and lungs resulting in coughing, wheezing, and shortness of breath.

Mechanism of Hg Toxicity

The precise mechanism by which Hg induces cell death is unclear as exposure to Hg interacts with a diverse array of intracellular targets. In general, the toxic actions of Hg primarily result from binding to free sulfhydryl groups leading to enzyme inhibition and a more generalized adverse condition. Hg is also capable of interacting with phosphoryl, carboxyl, amide, and amine groups, which leads to protein inactivity (Rafati-Rahimzadeh et al. 2014). Chronic exposure also results in ultrastructural changes within the mitochondria as well as inhibition of several mitochondrial enzymes causing depolarization of the mitochondria membrane, a reduction of ATP production and generation of ROS (Vergilio et al. 2015). Other modes of toxicity have been proposed for Hg-induced cell death including irreversible inhibition of selenoenzymes (Branco et al. 2012) and demyelination (Chu et al. 1998). Thus, the cellular effects of exposure to Hg are diverse and cell damage likely occurs by more than one mechanism, the effects of which may be additive or synergistic.

Hg Ototoxicity

Since most of the organic species of Hg absorbed are ultimately converted to the divalent cation in vivo, this review will focus on the available data regarding the deleterious actions of Hg^{2+} promoting cellular degeneration in the inner ear. A recent review comprehensively assessed the ototoxic effects of Hg (Hoshino et al. 2012). A total of 108 published studies were identified of which only 28 met the inclusion criteria set by the authors. All the articles reviewed revealed that exposure to Hg can produce hearing loss resulting from both peripheral and/or central damage. The basis for labeling deficits as mediated by the central auditory system were based on changes in the ABR and behavioral measures of central auditory processing whereas peripheral dysfunction was based on high-frequency audiometry. Unfortunately, few studies have actually attempted to directly assess the effects of Hg on the cochlea. In one study, inward and outward K^+ currents were measured in OHC using the whole-cell patch clamp technique (Liang et al. 2003); Hg was shown to affect K^+ currents in a voltage- and dose-dependent manner. Based on the fact that Hg is also a known inhibitor of the group I monovalent potassium cation pore-forming channels, the investigators examined whether high concentrations of Hg could affect the resting membrane potential. The results demonstrated that Hg at 1.0 – 100 mM is capable of depolarizing the resting membrane potential with a more pronounced effect on onset peak current than on steady-state end current. These findings suggest that Hg may lead to auditory transduction problems and hearing loss; however, it should be noted that the concentrations of Hg used greatly exceeded Hg levels seen in vivo. Another anatomical study noted that the earliest and most severe changes occurred in the sensory epithelium in the apex of the cochlea while the base was seldom damaged (Anniko and Sarkady 1978). Acute intoxication with Hg mostly affected both afferent and efferent nerve terminals and hair cells while chronic exposure also damaged the stria vascularis.

Histochemical examination of methylmercury poisoned rats (4 mg/kg/day for 16 days) demonstrated Hg deposits in the cerebellum and in parts of the vestibular nerves, cochlear nerves, spiral ganglion, and stria vascularis (Igarashi et al. 1992). In the vestibule, a small amount of Hg was seen in the acoustic maculae and in the cochlea and in only one instance was Hg detected in the organ of Corti. Based on the fact that there were no changes in the neurotransmitter levels of substance P in the inner ear as well as no other changes in pathology, it was concluded that methylmercury had little effect on inner ear function in contrast to the divalent species of Hg.

In summary, the majority of the clinical evidence supports the notion that excess Hg can lead to hearing impairment. This is not totally surprising given the very broad and nonspecific nature of the toxicological actions of the metal. Nevertheless, the actions of Hg are selective in regard to its deleterious behavior in the cochlea but, clearly, in order to establish the discriminating biochemical processes and the initial anatomical sites within the cochlea which are actually responsible for hearing loss requires additional study.

Summary

The cumulative findings based on the studies described above indicate that excess exposure to a variety of heavy metals can cause minor to severe hearing loss. Though this

can be regarded as only an inconsequential clinical deficit, it nevertheless does affect the quality of life for impaired individuals. Although overexposure is most often related to excess occupational contact, there are numerous instances where human error has led to major environmental catastrophes resulting in significant neurotoxic events.

The hearing impairment and lesions produced by heavy metals appear to be relatively selective as individual components within the cochlea are targeted by the different metals. Factors regulating selective cellular toxicity by the ionic forms of the heavy metals most likely include difference in transport processes by specific cell membrane carriers as well as the variations in the intracellular targets to which metals can interact. As noted in this review, the cellular binding sites for each of the metals responsible for initiating the selective cellular injury are unique, yet there are common downstream events that appear to be responsible for cell death. One of the most common end product responsible for cellular damage appears to be mitochondria dysfunction leading to increased oxidative stress. The initiating event provoking mitochondrial dysfunction may be direct via binding to essential mitochondrial components or as an indirect consequence of metal binding to other cellular constituents necessary for normal mitochondrial activity. Nevertheless, toxicity is highly selective though the consequential process most often manifests in apoptotic cell death.

In most cases, hearing loss induced by heavy metals is irreversible. Treatment, which includes removal from the noxious stimuli, at best only prevents subsequent damage to the auditory system especially since the half-lives of many of the metals are prolonged due to tight binding to intracellular sites. Chelation therapies, if exposure is caught early before damage to the inner ear has occurred, may be affective treatment but this has not been adequately examined.

Acknowledgments Research supported in part by grants from NIOSH R01 OH010235.

References

Adachi T, Aida K, Nishihara H, Kamiya T, Hara H (2011) Effect of hypoxia mimetic cobalt chloride on the expression of extracellular-superoxide dismutase in retinal pericytes. Biol Pharm Bull 34:1297–1300

Agirdir BV, Bilgen I, Dinc O, Ozcaglar HU, Fisenk F, Turhan M et al (2002) Effect of zinc ion on cadmium-induced auditory changes. Biol Trace Elem Res 88:153–163

Agrawal S, Flora G, Bhatnagar P, Flora SJ (2014) Comparative oxidative stress, metallothionein induction and organ toxicity following chronic exposure to arsenic, lead and mercury in rats. Cell Mol Biol (Noisy-le-grand) 60:13–21

Ahamed M, Siddiqui MK (2007) Low level lead exposure and oxidative stress: current opinions. Clin Chim Acta 383:57–64

Aimola P, Carmignani M, Volpe AR, Di Benedetto A, Claudio L, Waalkes MP et al (2012) Cadmium induces p53-dependent apoptosis in human prostate epithelial cells. PLoS ONE 7:e33647

Anderson M (1983) Mn ions pass through calcium channels. A possible explanation. J Gen Physiol 81:805–827

Anniko M, Sarkady L (1978) Cochlear pathology following exposure to mercury. Acta Otolaryngol 85:213–224

Antonini JM (2003) Health effects of welding. Crit Rev Toxicol 33:61–103

Antonini JM, Sriram K, Benkovic SA, Roberts JR, Stone S, Chen BT et al (2009) Mild steel welding fume causes manganese accumulation and subtle neuroinflammatory changes but not overt neuronal damage in discrete brain regions of rats after short-term inhalation exposure. Neurotoxicology 30:915–925

Antonini JM, Zeidler-Erdely PC, Young SH, Roberts JR, Erdely A (2012) Systemic immune cell response in rats after pulmonary exposure to manganese-containing particles collected from welding aerosols. J Immunotoxicol 9:184–192

Apostoli P, Catalani S, Zaghini A, Mariotti A, Poliani PL, Vielmi V et al (2013) High doses of cobalt induce optic and auditory neuropathy. Exp Toxicol Pathol 65:719–727

Banci L, Bertini I, Ciofi-Baffoni S, Su XC, Miras R, Bal N et al (2006) Structural basis for metal binding specificity: the N-terminal cadmium binding domain of the P1-type ATPase CadA. J Mol Biol 356:638–650

Basinger MA, Jones MM, Craft WD, Walker EM Jr, Sanders MM (1987) Chelating-agent suppression of cadmium-induced hepatotoxicity. J Toxicol Environ Health 22:261–271

Battaglia V, Compagnone A, Bandino A, Bragadin M, Rossi CA, Zanetti F et al (2009) Cobalt induces oxidative stress in isolated liver mitochondria responsible for permeability transition and intrinsic apoptosis in hepatocyte primary cultures. Int J Biochem Cell Biol 41:586–594

Bencko V, Cikrt M (1984) Manganese: a review of occupational and environmental toxicology. J Hyg Epidemiol Microbiol Immunol 28:139–148

Bertin G, Averbeck D (2006) Cadmium: cellular effects, modifications of biomolecules, modulation of DNA repair and genotoxic consequences (a review). Biochimie 88:1549–1559

Bouchard M, Mergler D, Baldwin ME, Panisset M (2008) Manganese cumulative exposure and symptoms: a follow-up study of alloy workers. Neurotoxicology 29:577–583

Bourre JM (2006) Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 1: micronutrients. J Nutr Health Aging 10:377–385

Bowler RM, Roels HA, Nakagawa S, Drezgic M, Diamond E, Park R et al (2007) Dose-effect relationships between manganese exposure and neurological, neuropsychological and pulmonary function in confined space bridge welders. Occup Environ Med 64:167–177

Bradberry SM, Wilkinson JM, Ferner RE (2014) Systemic toxicity related to metal hip prostheses. Clin Toxicol (Phila) 52:837–847

Branco V, Canario J, Lu J, Holmgren A, Carvalho C (2012) Mercury and selenium interaction in vivo: effects on thioredoxin reductase and glutathione peroxidase. Free Radic Biol Med 52:781–793

Bressler JP, Olivi L, Cheong JH, Kim Y, Bannona D (2004) Divalent metal transporter 1 in lead and cadmium transport. Ann N Y Acad Sci 1012:142–152

Burkhard PR, Delavelle J, Du Pasquier R, Spahr L (2003) Chronic Parkinsonism associated with cirrhosis: a distinct subset of acquired hepatocerebral degeneration. Arch Neurol 60:521–528

Chabicovsky M, Klepal W, Dallinger R (2004) Mechanisms of cadmium toxicity in terrestrial pulmonates: programmed cell

death and metallothionein overload. Environ Toxicol Chem 23:648–655
Chao JI, Yang JL (2001) Opposite roles of ERK and p38 mitogen-activated protein kinases in cadmium-induced genotoxicity and mitotic arrest. Chem Res Toxicol 14:1193–1202
Chatterjee S, Kundu S, Sengupta S, Bhattacharyya A (2009) Divergence to apoptosis from ROS induced cell cycle arrest: effect of cadmium. Mutat Res 663:22–31
Chen CJ, Liao SL (2002) Oxidative stress involves in astrocytic alterations induced by manganese. Exp Neurol 175:216–225
Choong G, Liu Y, Templeton DM (2014) Interplay of calcium and cadmium in mediating cadmium toxicity. Chem Biol Interact 211:54–65
Chu CC, Huang CC, Ryu SJ, Wu TN (1998) Chronic inorganic mercury induced peripheral neuropathy. Acta Neurol Scand 98:461–465
Chun HS, Lee H, Son JH (2001) Manganese induces endoplasmic reticulum (ER) stress and activates multiple caspases in nigral dopaminergic neuronal cells, SN4741. Neurosci Lett 316:5–8
Clarkson TW (1993) Mercury: major issues in environmental health. Environ Health Perspect 100:31–38
Counter SA, Buchanan LH (2002) Neuro-ototoxicity in Andean adults with chronic lead and noise exposure. J Occup Environ Med 44:30–38
Counter SA, Buchanan LH, Ortega F (2009a) Neurocognitive screening of lead-exposed andean adolescents and young adults. J Toxicol Environ Health A 72:625–632
Counter SA, Buchanan LH, Ortega F (2009b) Neurophysiologic and neurocognitive case profiles of Andean patients with chronic environmental lead poisoning. J Toxicol Environ Health A 72:1150–1159
Couper J (1837) On the effects of black oxide of manganese when inhaled into the lungs. Br Ann Med Pharm Vital Stat Gen Sci 1:41–42
Coutant A, Lebeau J, Bidon-Wagner N, Levalois C, Lectard B, Chevillard S (2006) Cadmium-induced apoptosis in lymphoblastoid cell line: involvement of caspase-dependent and -independent pathways. Biochimie 88:1815–1822
Da Silva CJDRAJ, Jeronymo S, Mendes MF, Milani FT, Maia AC, Jr Braga FT, Sens YA, Miorin LA (2007) A preliminary study revealing a new association in patients undergoing maintenance hemodialysis: manganism symptoms and T1 hyperintense changes in the basal ganglia. Am J Neuroradiol 28:1474–1479
Desole MS, Esposito G, Migheli R, Sircana S, Delogu MR, Fresu L et al (1997) Glutathione deficiency potentiates manganese toxicity in rat striatum and brainstem and in PC12 cells. Pharmacol Res 36:285–292
Dietrich KN, Succop PA, Berger OG, Keith RW (1992) Lead exposure and the central auditory processing abilities and cognitive development of urban children: the Cincinnati Lead Study cohort at age 5 years. Neurotoxicol Teratol 14:51–56
Ding J, Gong S (2004) The expression and significance of VIP and SP in the cochlea of rats. Lin Chuang Er Bi Yan Hou Ke Za Zhi 18(681–2):4
Ding D, Jiang H, Wang P, Salvi R (2007) Cell death after co-administration of cisplatin and ethacrynic acid. Hear Res 226:129–139
Ding D, Roth J, Salvi R (2011) Manganese is toxic to spiral ganglion neurons and hair cells in vitro. Neurotoxicology 32:233–241
Ding D, Salvi R, Roth JA (2014a) Cellular localization and developmental changes of the different isoforms of divalent metal transporter 1 (DMT1) in the inner ear of rats. Biometals 27:125–134
Ding D, Salvi R, Roth JA (2014b) Cellular localization and developmental changes of Zip8, Zip14 and transferrin receptor 1 in the inner ear of rats. Biometals 27:731–744
Donaldson JD, Beyersmann D (2005) Cobalt and cobalt compounds. Ulmann's encyclopedia of industrial chemistry. Wiley-VCH, Weinheim
Flora SJ (2002) Lead exposure: health effects, prevention and treatment. J Environ Biol 23:25–41
Fujishiro H, Yano Y, Takada Y, Tanihara M, Himeno S (2012) Roles of ZIP8, ZIP14, and DMT1 in transport of cadmium and manganese in mouse kidney proximal tubule cells. Metallomics 4:700–708
Garrick MD, Singleton ST, Vargas F, Kuo HC, Zhao L, Knopfel M et al (2006) DMT1: which metals does it transport? Biol Res 39:79–85
Garrick MD, Zhao L, Roth JA, Jiang H, Feng J, Foot NJ et al (2012) Isoform specific regulation of divalent metal (ion) transporter (DMT1) by proteasomal degradation. Biometals 25:787–793
Garza A, Vega R, Soto E (2006) Cellular mechanisms of lead neurotoxicity. Med Sci Monit 12:RA57–RA65
Gavin CE, Gunter KK, Gunter TE (1990) Manganese and calcium efflux kinetics in brain mitochondria. Relevance to manganese toxicity. Biochem J 266:329–334
Gavin CE, Gunter KK, Gunter TE (1999) Manganese and calcium transport in mitochondria: implications for manganese toxicity. Neurotoxicology 20:445–453
Hamada T, Tanimoto A, Sasaguri Y (1997) Apoptosis induced by cadmium. Apoptosis 2:359–367
Hauser RA, Zesiewicz TA (1996) Manganese and chronic liver disease. Mov Disord 11:589
Hauser RA, Zesiewicz TA, Rosemurgy AS, Martinez C, Olanow CW (1994) Manganese intoxication and chronic liver failure. Ann Neurol 36:871–875
Herber RF (1992) The World Health Organization study on health effects of exposure to cadmium: morbidity studies. IARC Sci Publ 118:347–358
Hirata Y, Adachi K, Kiuchi K (1998) Activation of JNK pathway and induction of apoptosis by manganese in PC12 cells. J Neurochem 71:1607–1615
Hoshino AC, Ferreira HP, Malm O, Carvallo RM, Camara VM (2012) A systematic review of mercury ototoxicity. Cad Saude Publica 28:1239–1248
Hsu PC, Liu MY, Hsu CC, Chen LY, Guo YL (1997) Lead exposure causes generation of reactive oxygen species and functional impairment in rat sperm. Toxicology 122:133–143
Huang CC, Lu CS, Chu NS, Hochberg F, Lilienfeld D, Olanow W et al (1993) Progression after chronic manganese exposure. Neurology 43:1479–1483
Huang PC, Su PH, Chen HY, Huang HB, Tsai JL, Huang HI et al (2012) Childhood blood lead levels and intellectual development after ban of leaded gasoline in Taiwan: a 9-year prospective study. Environ Int 40:88–96
Huff J, Lunn RM, Waalkes MP, Tomatis L, Infante PF (2007) Cadmium-induced cancers in animals and in humans. Int J Occup Environ Health 13:202–212
Humes HD (1999) Insights into ototoxicity. Analogies to nephrotoxicity. Ann N Y Acad Sci 884:15–18
Hurley LS (1981) The roles of trace elements in foetal and neonatal development. Philos Trans R Soc Lond B Biol Sci 294:145–152
Igarashi S, Koide C, Sasaki H, Nakano Y (1992) Mercury deposition and its relationship to inner ear function in methylmercury-poisoned rats. A histological and immunohistochemical study. Acta Otolaryngol 112:773–778
Ikeda T, Takahashi K, Kabata T, Sakagoshi D, Tomita K, Yamada M (2010) Polyneuropathy caused by cobalt-chromium metallosis after total hip replacement. Muscle Nerve 42:140–143
Illing AC, Shawki A, Cunningham CL, Mackenzie B (2012) Substrate profile and metal-ion selectivity of human divalent metal-ion transporter-1. J Biol Chem 287:30485–30496

Jenkitkasemwong S, Wang CY, Mackenzie B, Knutson MD (2012) Physiologic implications of metal-ion transport by ZIP14 and ZIP8. Biometals 25:643–655

Jones LG, Prins J, Park S, Walton JP, Luebke AE, Lurie DI (2008) Lead exposure during development results in increased neurofilament phosphorylation, neuritic beading, and temporal processing deficits within the murine auditory brainstem. J Comp Neurol 506:1003–1017

Josephs KA, Ahlskog JE, Klos KJ, Kumar N, Fealey RD, Trenerry MR et al (2005) Neurologic manifestations in welders with pallidal MRI T1 hyperintensity. Neurology 64:2033–2039

Kannurpatti SS, Joshi PG, Joshi NB (2000) Calcium sequestering ability of mitochondria modulates influx of calcium through glutamate receptor channel. Neurochem Res 25:1527–1536

Karovic O, Tonazzini I, Rebola N, Edstrom E, Lovdahl C, Fredholm BB et al (2007) Toxic effects of cobalt in primary cultures of mouse astrocytes. Similarities with hypoxia and role of HIF-1alpha. Biochem Pharmacol 73:694–708

Keen CL, Ensunsa JL, Watson MH, Baly DL, Donovan SM, Monaco MH et al (1999) Nutritional aspects of manganese from experimental studies. Neurotoxicology 20:213–223

Kemmerer AR, Elvehjem CA, Hart EB (1931) Studies on the relation of manganese to the nutrition of the mouse. J Biol Chem 92:623–630

Khalkova Z, Kostadinova G (1986) Auditory-vestibular changes in workers in ferrous metallurgy manufacture. Probl Khig 11:134–138

Kim HJ, Yang SJ, Kim YS, Kim TU (2003) Cobalt chloride-induced apoptosis and extracellular signal-regulated protein kinase activation in human cervical cancer HeLa cells. J Biochem Mol Biol 36:468–474

Kim SJ, Jeong HJ, Myung NY, Kim MC, Lee JH, So HS et al (2008) The protective mechanism of antioxidants in cadmium-induced ototoxicity in vitro and in vivo. Environ Health Perspect 116:854–862

Kim SJ, Shin BG, Choi IY, Kim DH, Kim MC, Myung NY et al (2009) Hwanggunchungyitang prevents cadmium-induced ototoxicity through suppression of the activation of caspase-9 and extracellular signal-related kinase in auditory HEI-OC1 cells. Biol Pharm Bull 32:213–219

Kitazawa M, Anantharam V, Yang Y, Hirata Y, Kanthasamy A, Kanthasamy AG (2005) Activation of protein kinase C delta by proteolytic cleavage contributes to manganese-induced apoptosis in dopaminergic cells: protective role of Bcl-2. Biochem Pharmacol 69:133–146

Koizumi T, Shirakura H, Kumagai H, Tatsumoto H, Suzuki KT (1996) Mechanism of cadmium-induced cytotoxicity in rat hepatocytes: cadmium-induced active oxygen-related permeability changes of the plasma membrane. Toxicology 114:125–134

Korczynski RE (2000) Occupational health concerns in the welding industry. Appl Occup Environ Hyg 15:936–945

Krieger D, Krieger S, Jansen O, Gass P, Theilmann L, Lichtnecker H (1995) Manganese and chronic hepatic encephalopathy. Lancet 346:270–274

Kuriyama H, Jenkins O, Altschuler RA (1994) Immunocytochemical localization of AMPA selective glutamate receptor subunits in the rat cochlea. Hear Res 80:233–240

Lasfer M, Vadrot N, Aoudjehane L, Conti F, Bringuier AF, Feldmann G et al (2008) Cadmium induces mitochondria-dependent apoptosis of normal human hepatocytes. Cell Biol Toxicol 24:55–62

Leonard S, Gannett PM, Rojanasakul Y, Schwegler-Berry D, Castranova V, Vallyathan V et al (1998) Cobalt-mediated generation of reactive oxygen species and its possible mechanism. J Inorg Biochem 70:239–244

Li Y, Ding D, Jiang H, Fu Y, Salvi R (2011) Co-administration of cisplatin and furosemide causes rapid and massive loss of cochlear hair cells in mice. Neurotox Res 20:307–319

Li P, Ding D, Salvi R, Roth JA (2015) Cobalt-induced ototoxicity in rat postnatal cochlear organotypic cultures. Neurotox Res 28:209–221

Liang GH, Jarlebark L, Ulfendahl M, Moore EJ (2003) Mercury (Hg2+) suppression of potassium currents of outer hair cells. Neurotoxicol Teratol 25:349–359

Lidsky TI, Schneider JS (2003) Lead neurotoxicity in children: basic mechanisms and clinical correlates. Brain 126:5–19

Liu S, Zhang K, Wu S, Ji X, Li N, Liu R et al (2011) Lead-induced hearing loss in rats and the protective effect of copper. Biol Trace Elem Res 144:1112–1119

Liu X, Zheng G, Wu Y, Shen X, Jing J, Yu T et al (2013) Lead exposure results in hearing loss and disruption of the cochlear blood–labyrinth barrier and the protective role of iron supplement. Neurotoxicology 39:173–181

Liu H, Ding D, Sun H, Jiang H, Wu X, Roth JA et al (2014) Cadmium-induced ototoxicity in rat cochlear organotypic cultures. Neurotox Res 26:179–189

Lobarinas E, Salvi R, Ding D (2013) Insensitivity of the audiogram to carboplatin induced inner hair cell loss in chinchillas. Hear Res 302:113–120

Lopes AC, Peixe TS, Mesas AE, Paoliello MM (2016) Lead exposure and oxidative stress: a systematic review. Rev Environ Contam Toxicol 236:193–238

Lucchini RG, Martin CJ, Doney BC (2009) From manganism to manganese-induced parkinsonism: a conceptual model based on the evolution of exposure. Neuromol Med 11:311–321

Ma C, Schneider SN, Miller M, Nebert DW, Lind C, Roda SM et al (2008) Manganese accumulation in the mouse ear following systemic exposure. J Biochem Mol Toxicol 22:305–310

Malva JO, Vieira AP, Ambrosio AF, Oliveira CR (2003) Cobalt staining of hippocampal neurons mediated by non-desensitizing activation of AMPA but not kainate receptors. NeuroReport 14:847–850

Martinez-Finley EJ, Gavin CE, Aschner M, Gunter TE (2013) Manganese neurotoxicity and the role of reactive oxygen species. Free Radic Biol Med 62:65–75

Mason LH, Harp JP, Han DY (2014) Pb neurotoxicity: neuropsychological effects of lead toxicity. Biomed Res Int 2014: 840547

Messner B, Turkcan A, Ploner C, Laufer G, Bernhard D (2015) Cadmium overkill: autophagy, apoptosis and necrosis signalling in endothelial cells exposed to cadmium. Cell Mol Life Sci 73(8):1699–1713

Needleman HL (2000) The removal of lead from gasoline: historical and personal reflections. Environ Res 84:20–35

Nikolov Z (1974) Hearing reduction caused by manganese and noise. JFORL J Fr Otorhinolaryngol Audiophonol Chir Maxillofac 23:231–234

Nogawa K, Yamada Y, Honda R, Ishizaki M, Tsuritani I, Kawano S et al (1983) The relationship between itai-itai disease among inhabitants of the Jinzu River basin and cadmium in rice. Toxicol Lett 17:263–266

Olanow CW, Good PF, Shinotoh H, Hewitt KA, Vingerhoets F, Snow BJ et al (1996) Manganese intoxication in the rhesus monkey: a clinical, imaging, pathologic, and biochemical study. Neurology 46:492–498

Oldenburg M, Wegner R, Baur X (2009) Severe cobalt intoxication due to prosthesis wear in repeated total hip arthroplasty. J Arthroplasty 24(825):e15–e20

Orent ER, McCollum EV (1931) Effects of deprivation of manganese in the rat. J Biol Chem 92:661–678

Osman K, Pawlas K, Schutz A, Gazdzik M, Sokal JA, Vahter M (1999) Lead exposure and hearing effects in children in Katowice, Poland. Environ Res 80:1–8

Otto DA, Fox DA (1993) Auditory and visual dysfunction following lead exposure. Neurotoxicology 14:191–207

Ozcaglar HU, Agirdir B, Dinc O, Turhan M, Kilincarslan S, Oner G (2001) Effects of cadmium on the hearing system. Acta Otolaryngol 121:393–397

Pal PK, Samii A, Calne DB (1999) Manganese neurotoxicity: a review of clinical features, imaging and pathology. Neurotoxicology 20:227–238

Pande M, Flora SJ (2002) Lead induced oxidative damage and its response to combined administration of alpha-lipoic acid and succimers in rats. Toxicology 177:187–196

Park RM, Bowler RM, Eggerth DE, Diamond E, Spencer KJ, Smith D et al (2006) Issues in neurological risk assessment for occupational exposures: the Bay Bridge welders. Neurotoxicology 27:373–384

Paustenbach DJ, Tvermoes BE, Unice KM, Finley BL, Kerger BD (2013) A review of the health hazards posed by cobalt. Crit Rev Toxicol 43:316–362

Pelclova D, Sklensky M, Janicek P, Lach K (2012) Severe cobalt intoxication following hip replacement revision: clinical features and outcome. Clin Toxicol (Phila) 50:262–265

Permenter MG, Dennis WE, Sutto TE, Jackson DA, Lewis JA, Stallings JD (2013) Exposure to cobalt causes transcriptomic and proteomic changes in two rat liver derived cell lines. PLoS ONE 8:e83751

Petit A, Mwale F, Zukor DJ, Catelas I, Antoniou J, Huk OL (2004) Effect of cobalt and chromium ions on bcl-2, bax, caspase-3, and caspase-8 expression in human U937 macrophages. Biomaterials 25:2013–2018

Pinilla-Tenas JJ, Sparkman BK, Shawki A, Illing AC, Mitchell CJ, Zhao N et al (2011) Zip14 is a complex broad-scope metal-ion transporter whose functional properties support roles in the cellular uptake of zinc and nontransferrin-bound iron. Am J Physiol Cell Physiol 301:C862–C871

Pizon AF, Abesamis M, King AM, Menke N (2013) Prosthetic hip-associated cobalt toxicity. J Med Toxicol 9:416–417

Pomier-Layrargues G, Spahr L, Butterworth RF (1995) Increased manganese concentrations in pallidum of cirrhotic patients. Lancet 345:735

Prasher D (2009) Heavy metals and noise exposure: health effects. Noise Health 11:141–144

Prozialeck WC, Edwards JR, Vaidya VS, Bonventre JV (2009) Preclinical evaluation of novel urinary biomarkers of cadmium nephrotoxicity. Toxicol Appl Pharmacol 238:301–305

Qi W, Ding D, Salvi RJ (2008) Cytotoxic effects of dimethyl sulphoxide (DMSO) on cochlear organotypic cultures. Hear Res 236:52–60

Qi W, Ding D, Zhu H, Lu D, Wang Y, Ding J et al (2014) Efficient siRNA transfection to the inner ear through the intact round window by a novel proteidic delivery technology in the chinchilla. Gene Ther 21:10–18

Quadri M, Federico A, Zhao T, Breedveld GJ, Battisti C, Delnooz C et al (2012) Mutations in SLC30A10 cause Parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease. Am J Hum Genet 90:467–477

Rabenstein DL, Isab AA (1982) A proton nuclear magnetic resonance study of the interaction of mercury with intact human erythrocytes. Biochim Biophys Acta 721:374–384

Rafati-Rahimzadeh M, Rafati-Rahimzadeh M, Kazemi S, Moghadamnia AA (2014) Current approaches of the management of mercury poisoning: need of the hour. Daru 22:46

Rehfisch P, Anderson M, Berg P, Lampa E, Nordling Y, Svartengren M et al (2012) Lung function and respiratory symptoms in hard metal workers exposed to cobalt. J Occup Environ Med 54:409–413

Rice KM, Walker EM Jr, Wu M, Gillette C, Blough ER (2014) Environmental mercury and its toxic effects. J Prev Med Public Health 47:74–83

Rigon AP, Cordova FM, Oliveira CS, Posser T, Costa AP, Silva IG et al (2008) Neurotoxicity of cadmium on immature hippocampus and a neuroprotective role for p38 MAPK. Neurotoxicology 29:727–734

Roth JA (2006) Homeostatic and toxic mechanisms regulating manganese uptake, retention, and elimination. Biol Res 39:45–57

Roth JA, Feng L, Walowitz J, Browne RW (2000) Manganese-induced rat pheochromocytoma (PC12) cell death is independent of caspase activation. J Neurosci Res 61:162–171

Roth JA, Horbinski C, Higgins D, Lein P, Garrick MD (2002) Mechanisms of manganese-induced rat pheochromocytoma (PC12) cell death and cell differentiation. Neurotoxicology 23:147–157

Roth J, Ponzoni S, Aschner M (2013) Manganese homeostasis and transport. Met Ions Life Sci 12:169–201

Rovetta F, Stacchiotti A, Faggi F, Catalani S, Apostoli P, Fanzani A et al (2013) Cobalt triggers necrotic cell death and atrophy in skeletal C2C12 myotubes. Toxicol Appl Pharmacol 271:196–205

Ruel J, Chen C, Pujol R, Bobbin RP, Puel JL (1999) AMPA-preferring glutamate receptors in cochlear physiology of adult guinea-pig. J Physiol 518(Pt 3):667–680

Sallmen M (2001) Exposure to lead and male fertility. Int J Occup Med Environ Health 14:219–222

Salvi R, Lobarinas E, Sun W (2009) Overview of anatomy and physiology of the peripheral auditory system. In: Chaisin M (ed) Hearing loss and musicians: prevention and management. Plural Publishers, San Diego, pp 11–29

Sanders T, Liu Y, Buchner V, Tchounwou PB (2009) Neurotoxic effects and biomarkers of lead exposure: a review. Rev Environ Health 24:15–45

Santamaria AB, Sulsky SI (2010) Risk assessment of an essential element: manganese. J Toxicol Environ Health A 73:128–155

Saric M, Piasek M (2000) Environmental exposure to manganese and combined exposure to gaseous upper respiratory irritants: mechanism of action and adverse health effects. Rev Environ Health 15:413–419

Sarkar A, Bhagat J, Ingole BS, Rao DP, Markad VL (2015) Genotoxicity of cadmium chloride in the marine gastropod *Nerita chamaeleon* using comet assay and alkaline unwinding assay. Environ Toxicol 30:177–187

Scharf B, Clement CC, Zolla V, Perino G, Yan B, Elci SG et al (2014) Molecular analysis of chromium and cobalt-related toxicity. Sci Rep 4:5729

Schaumberg DA, Mendes F, Balaram M, Dana MR, Sparrow D, Hu H (2004) Accumulated lead exposure and risk of age-related cataract in men. JAMA 292:2750–2754

Schmutzhard J, Kositz CH, Glueckert R, Schmutzhard E, Schrott-Fischer A, Lackner P (2012) Apoptosis of the fibrocytes type 1 in the spiral ligament and blood labyrinth barrier disturbance cause hearing impairment in murine cerebral malaria. Malar J 11:30

Schrantz N, Blanchard DA, Mitenne F, Auffredou MT, Vazquez A, Leca G (1999) Manganese induces apoptosis of human B cells: caspase-dependent cell death blocked by bcl-2. Cell Death Differ 6:445–453

Schwartz J, Otto D (1987) Blood lead, hearing thresholds, and neurobehavioral development in children and youth. Arch Environ Health 42:153–160

Seghizzi P, D'Adda F, Borleri D, Barbic F, Mosconi G (1994) Cobalt myocardiopathy. A critical review of literature. Sci Total Environ 150:105–109

Shi LZ, Zheng W (2007) Early lead exposure increases the leakage of the blood–cerebrospinal fluid barrier, in vitro. Hum Exp Toxicol 26:159–167

Simonsen LO, Brown AM, Harbak H, Kristensen BI, Bennekou P (2011) Cobalt uptake and binding in human red blood cells. Blood Cells Mol Dis 46:266–276

Simonsen LO, Harbak H, Bennekou P (2012) Cobalt metabolism and toxicology—a brief update. Sci Total Environ 432:210–215

Sousa CA, Soares EV (2014) Mitochondria are the main source and one of the targets of Pb (lead)-induced oxidative stress in the yeast *Saccharomyces cerevisiae*. Appl Microbiol Biotechnol 98:5153–5160

Staudinger KC, Roth VS (1998) Occupational lead poisoning. Am Fam Physician 57(719–26):31–32

Strause LG, Hegenauer J, Saltman P, Cone R, Resnick D (1986) Effects of long-term dietary manganese and copper deficiency on rat skeleton. J Nutr 116:135–141

Sutto TE (2011) Prioritization of the oral (ingestive) hazard of industrial chemicals. Prioritization of the oral (ingestive) hazard of industrial chemicals. Naval Research Laboratory, Washington, DC

Swennen B, Buchet JP, Stanescu D, Lison D, Lauwerys R (1993) Epidemiological survey of workers exposed to cobalt oxides, cobalt salts, and cobalt metal. Br J Ind Med 50:835–842

Syversen T, Kaur P (2012) The toxicology of mercury and its compounds. J Trace Elem Med Biol 26:215–226

Tuschl K, Clayton PT, Gospe SM Jr, Gulab S, Ibrahim S, Singhi P et al (2012) Syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia caused by mutations in SLC30A10, a manganese transporter in man. Am J Hum Genet 90:457–466

Vaziri ND, Gonick HC (2008) Cardiovascular effects of lead exposure. Indian J Med Res 128:426–435

Vazquez M, Velez D, Devesa V, Puig S (2015) Participation of divalent cation transporter DMT1 in the uptake of inorganic mercury. Toxicology 331:119–124

Vergilio CS, Carvalho CE, Melo EJ (2015) Mercury-induced dysfunctions in multiple organelles leading to cell death. Toxicol In Vitro 29:63–71

Viaene MK, Roels HA, Leenders J, De Groof M, Swerts LJ, Lison D et al (1999) Cadmium: a possible etiological factor in peripheral polyneuropathy. Neurotoxicology 20:7–16

Viaene MK, Masschelein R, Leenders J, De Groof M, Swerts LJ, Roels HA (2000) Neurobehavioural effects of occupational exposure to cadmium: a cross sectional epidemiological study. Occup Environ Med 57:19–27

Wang SH, Shih YL, Ko WC, Wei YH, Shih CM (2008) Cadmium-induced autophagy and apoptosis are mediated by a calcium signaling pathway. Cell Mol Life Sci 65:3640–3652

Wang Q, Luo W, Zhang W, Liu M, Song H, Chen J (2011) Involvement of DMT1 + IRE in the transport of lead in an in vitro BBB model. Toxicol In Vitro 25:991–998

Wang CY, Jenkitkasemwong S, Duarte S, Sparkman BK, Shawki A, Mackenzie B et al (2012) ZIP8 is an iron and zinc transporter whose cell-surface expression is up-regulated by cellular iron loading. J Biol Chem 287:34032–34043

Watrach AM (1964) Degeneration of mitochondria in lead poisoning. J Ultrastruct Res 10:177–181

Weisskopf MG, Proctor SP, Wright RO, Schwartz J, Spiro A 3rd, Sparrow D et al (2007) Cumulative lead exposure and cognitive performance among elderly men. Epidemiology 18:59–66

Whitworth CA, Hudson TE, Rybak LP (1999) The effect of combined administration of cadmium and furosemide on auditory function in the rat. Hear Res 129:61–70

Xu C, Johnson JE, Singh PK, Jones MM, Yan H, Carter CE (1996) In vivo studies of cadmium-induced apoptosis in testicular tissue of the rat and its modulation by a chelating agent. Toxicology 107:1–8

Xue-wen W, Ding D, Hong S, Hong L, Hai-yan J, Salvi R (2011) Lead neurotoxicity in rat cochlear organotypic cultures. J Otol 6(2):45–50

Yamada K (2013) Cobalt: its role in health and disease. Met Ions Life Sci 13:295–320

Yamamura K, Terayama K, Yamamoto N, Kohyama A, Kishi R (1989) Effects of acute lead acetate exposure on adult guinea pigs: electrophysiological study of the inner ear. Fundam Appl Toxicol 13:509–515