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# Chemical exposure and hearing loss☆

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## Introduction

Workers are commonly exposed to multiple factors and substances that are hazardous to health. For instance, in 2005, approximately 30% of the European workers reported being exposed to noise during at least a quarter of the time spent in their work environment, 11% reported inhaling vapors such as solvents and thinners; 19% reported exposure to smoke, fumes, powder, or dust; and 14% reported handling chemical substances.[1] Although occupational noise exposure has long been recognized in the United States and in Europe as the most deleterious factor to hearing[2,3] the impact of chemical-induced hearing loss on workers should not be underestimated.[4] A cursory survey of the literature for the last three decades reveals that concern about the effects of chemicals on hearing has grown steadily. The proliferation of work-related substances and medicinal drugs (mostly antitumor drugs and aminoglycosides) has been accompanied by an equivalent increase in the number of scientific publications on the hearing risks encountered by chemical-exposed persons. Cause for concern is even greater when the synergistic risks of co-exposures are considered. For example, physiological factors may increase the severity of a chemical's effect on hearing. Today, robust evidence also confirms that the effects of ototoxic substances on ear function can be aggravated by noise, which remains a well-recognized cause of hearing impairment. In an expert forecast supervised by the European Agency for Safety and Health at Work[5] (EU-OSHA, 2009), a "combined exposure to noise and ototoxic substances" was rated as an emerging risk.

Industrial ototoxic chemicals have predominantly been assessed through animal studies, which are supported by data from epidemiologic studies on human workers from various industries. Bergström and Nyström (1986) published the seminal results of a 20-year longitudinal study performed with 319 Swedish employees from different industrial sectors.[2] This study began in 1958 and involved testing workers' hearing regularly. Its findings showed that a large proportion (23%) of the employees working in a chemical division suffered from hearing impairment, despite their exposure to lower noise levels than other divisions. Based on this type of evidence, researchers have long hypothesized that industrial solvents pose an additive risk to hearing. Scientific findings in animals are generally considered qualitatively relevant to human health, provided no substantial difference in biological response (e.g. metabolism) exists between test animals and humans. Despite these findings, current research is limited by the following:

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1. a lack of detailed exposure histories;
2. the presence of confounding factors (ototoxic drugs, tobacco, alcohol consumption, aging, and exposures outside the workplace);
3. and the fact that chemical exposure scenarios used in experimental investigations are qualitatively different from real-world occupational settings.

In this extensive, but not exhaustive, review of the literature, the authors hope to share the evidence indicating that noise is not the only source of work-related hearing damage and to draw greater attention to the matter of chemically induced hearing loss. The present publication intends to provide occupational physicians and other health professionals with a clear picture of what is known about how chemical substances may affect hearing ability in the general population, and more specifically, in workers. The article describes the following:

1. chemicals that can be noxious to the inner ear;
2. work areas where exposure to ototoxic substances are likely;
3. and the basic features of the physiological mechanisms leading to hearing impairment.

This article also addresses the limitations of pure-tone air-conduction audiometry when assessing chemical-induced hearing loss and proposes a more complete approach to evaluate the auditory neurosensory hearing receptor and the neural pathways involved in the stapedial reflex. With the proposed battery of tests, physicians will be able to evaluate both ototoxicity and neurotoxicity. Throughout this manuscript, emphasis is placed on the need for stronger links between primary care and occupational physicians. This could help preserve patients' hearing status as a part of their overall health.

## Ototoxic drugs

It is well documented that some medicinal drugs, such as powerful antibiotics and anti-neoplastic drugs used against life-threatening diseases can cause auditory and/or vestibular dysfunction in patients. Functional damage can include permanent hearing loss and tinnitus. In several countries, administration of these drugs is monitored, and guidelines are available online (AAA, 2009, available online at http://www.audiology.org/resources/documentlibrary/Pages/OtotoxicityMonitoring.aspx). A brief review of these substances is presented in the section Which substances can be considered ototoxic?, but first we review some of the terms used to describe how they affect hearing and their definitions.

### Definitions

Noise is a physical factor that causes mostly mechanical and metabolic damage to the peripheral auditory receptor, the cochlea, and more rarely, to the auditory neural pathways.[6–8] In contrast, chemicals in the bloodstream go through either the blood-labyrinth barrier into the cochlea or the blood–brain barrier to reach the eighth cranial nerve and the central nervous system.[9–13] As a result, chemical-induced hearing loss can be the result of effects on several sites within the hearing system. Ototoxic chemicals may affect the

structures and/or the function of the inner ear (auditory and vestibular apparatus) and the connected neural pathways. From a general point of view, both cochleotoxicants and vestibulotoxicants can be defined as ototoxicants.

A cochleotoxicant can affect different cochlear structures, including the auditory sensory cells ("hair cells"), the fluid-producing cell layer on the outer wall of the cochlear duct ("stria vascularis"), and the spiral ganglion cells. In most cases, cochlear hair cells are the primary targets of cochleotoxicants (Figs. 1–5).

## Which substances can be considered ototoxic?

This article only reviews chemicals for which the strongest evidence of ototoxicity exists. A substance was included if human data are available, or if two well-documented animal studies reported clear and reliable findings in a coherent manner. If supporting human data were lacking, species-specific features should not contradict extrapolation of animal findings to humans. For the sake of clarity, data on potentially ototoxic substances are not reported in the present article.

**Aminoglycosides—**The aminoglycosides, such as streptomycin, kanamycin, neomycin, gentamicin, tobramycin, amikacin, and netilmicin are commonly used to treat gram-negative bacterial infections. Unfortunately, the clinical benefits of these agents can be outweighed by their toxicity, which includes cochlear damage. The incidence of hearing loss ranges from a few percent to up to 33% of the aminoglycoside-treated patients. Aminoglycoside-induced hearing loss spreads from high to low frequencies depending on the duration of treatment and the dose. After systemic administration, the antibiotics rapidly go through the blood–labyrinth barrier at the level of the stria vascularis to penetrate the cochlea. The drug reaches the perilymph and thereby the outer hair cells, which are particularly sensitive to antibiotics.[14–17] They can remain in the cochlea for several months after discontinuing the treatment.[18,19] Because of this long clearance time from the inner-ear liquids, occupational physicians must take aminoglycoside treatment into account as, after hospitalization, an employee could return to work with aminoglycoside-contaminated cochlea, which would make them particularly vulnerable to noise. An innocuous noise exposure can become noxious with aminoglycosides.[20] Consequently, good communication between primary care and occupational physicians is required to avoid dangerous co-exposures to noise and aminoglycosides. Before their return to work, the company physician should examine anyone who has been hospitalized, or anyone who was treated with antibiotics to determine the nature of the drugs. Unfortunately, monitoring the serum aminoglycoside level is not sufficient to prevent a likely co-exposure since these antibiotics take longer to clear from the perilymph (inner-ear liquids) than from the blood. A safer approach would be to protect employees from an unexpected co-exposure to noise and aminoglycosides for at least 3 months after the end of the treatment.

**Mechanism of aminoglycoside ototoxicity—**Aminoglycosides penetrate the outer hair cells from the endolymph. They do not cause lipid peroxidation by themselves; however, they form an aminoglycoside–iron complex that interacts with polyphosphoinositides. This reaction increases membrane permeability and generates the

release of reactive oxygen species (ROS) through the oxidation of arachidonic acid (breakdown products) in membranes. Superoxide, hydroxyl radical, and hydrogen peroxide then activate the c-Jun N-terminal kinase (JNK) pathway, which can translocate to the nucleus to activate genes involved in the cell death pathway. The products of these genes translocate to the mitochondria, where they induce the release of cytochrome c, which triggers apoptosis via caspases. Cell death may also result from caspase-independent mechanisms.[21]

**Anti-neoplastic drugs—**Platinum-derivates such as cisplatin and carboplatin are anticancer drugs that have ototoxic side effects.[22–24] The ototoxicity induced by platinum-derivates is characterized by the loss of cochlear hair cells and cells of the spiral ganglion and by degeneration of the stria vascularis.[25] As with aminoglycosides, hearing impairment induced by platinum-derivates covers the range from high to low frequencies.[26] An exacerbation of cisplatin ototoxicity was observed with exposure to concomitant moderate to high noise levels in chinchilla and guinea pigs.[27,28]

**Loop diuretics—**Ethacrynic acid, furosemide, and bumetanide are three loop diuretics widely used to increase the volume of urine excretion as part of the treatment for high blood pressure and swelling due to congestive heart failure. They act on the ascending limb of the loop of Henle, inhibiting sodium- and chloride-ion reabsorption in the kidney. In the mean time, diuretics act on the sodium- and potassium-transporters/pumps located within the stria vascularis, disturbing the ionic concentration of endolymph. Therefore, there is a parallel effect of diuretics on kidney and ear. Hearing loss is a temporary side effect that lasts only during the treatment. The effect is characterized by a sudden high-frequency hearing loss due to dysfunctions of the stria vascularis. These dysfunctions affect the ionic gradients between the endolymph and the perilymph, decreasing endocochlear potential and thereby sensorial transduction.[29–31]

Toxic interactions of loop diuretics and other known ototoxic drugs have been well documented, particularly with aminoglycosides. Dysfunctions at the level of the stria vascularis may result in a massive entry of aminoglycosides into the inner-ear fluid.[32] Thus, the effect of loop diuretics on the stria vascularis facilitates the toxic effects of aminoglycosides on the hair cells. Similarly, ethacrynic acid is known to interact with cisplatin to increase its ototoxic effects.[33] Finally, results from a study in rats showed that the ototoxic effect of cadmium may be potentiated by furosemide.[34]

**Acetyl salicylic acid—**High doses of acetyl salicylic acid (aspirin;>2.5 g/day) may induce a temporary auditory threshold shift and sometimes tinnitus.[35,36] In general, recovery of normal auditory sensitivity occurs within 2 or 3 days of discontinuing salicylate administration. The exact mechanism of salicylate-induced hearing impairments remains incompletely known. The ototoxic effects seem to result from a combination of several reversible cochlear disturbances.[37] Like aspirin, many other painkillers and antipyretics (quinine and chloroquine) are recognized for their potential ototoxic side effects. Salicylate-induced temporary threshold shifts may exacerbate the temporary effects of noise, hamper speech discrimination, and increase difficulty in detecting an alarm sounding in a noisy environment.[38,39]

## Work-related substances

In many industries workers are exposed to both noise and chemicals, these include printing, painting, boat building, construction, glue manufacturing, metal products, chemicals, petroleum, leather products, furniture making, agriculture, and mining.[1] In addition, some public safety workers, like firefighters, are also exposed to both noise and chemicals. Environmental exposure studies have determined the concentration of combustion products and various toxic agents in the smoke to which firefighters may be exposed.[40–44] According to these studies, smoke contains numerous harmful chemicals such as acrolein, benzene, methylene chloride, polyaromatic hydrocarbons, perchloroethylene, carbon monoxide, toluene, trichloroethylene, trichlorophenol, xylene, and formaldehyde. In addition, combustion products include metals such as lead, cadmium, mercury, and arsenic. Common sources of these metals in structural and vehicle fires include lead (old paint and PVC), cadmium (batteries and PVC), mercury (thermostats, automotive switches and thermometers), and arsenic (pressure-treated wood).[45,46] Many of the compounds detected in smoke from fires are also known to be neurotoxic or ototoxic.

### Aromatic solvents

Toluene and styrene are the most widely and extensively used aromatic solvents in industry.[47] Toluene is a major component of adhesives, paints, lacquers, varnishes, printing inks, degreasers, fuel additives, glues and thinners, whereas styrene is present when manufacturing plastics, rubber articles, and glass fibers.[48]

Chronic exposure to these aromatic solvents can affect the central nervous system[49,50,11] and also the inner ear.[51,52] The cochleotoxic effects of aromatic solvents such as toluene, styrene, ethylbenzene, p-xylene, various methylstyrenes, allylbenzene, and n-propylbenzene have been repeatedly demonstrated in animal experiments.[53–57] Long-duration exposures to aromatic solvents have been shown to cause irreversible hearing impairment, with the cochlear hair cells as the first targets.[58,59] Most of these animal studies were performed with rats, whose cochleae are sensitive to aromatic solvents.[60,61] Because of their similar metabolism, rats are considered comparatively good animal models for investigating the potential ototoxic properties of aromatic solvents in humans.[62]

**Mechanisms of aromatic solvent ototoxicity—**Aromatic solvents most likely affect hearing through chemical poisoning of hair cells, resulting in disorganization of their membranous structures.[54] An acute effect may be caused by the direct action of solvents on the cells of the organ of Corti, whereas chronic ototoxic effects may be explained by the formation of chemically and biologically reactive intermediates. These intermediates include reactive oxygen species, which may trigger the death of these cells.[63] They can also provoke dysfunctions of transmembrane $K^+$ fluxes, which play a determining role in the physiology of hair cells during acoustic stimulation.[64] During acoustic stimulation, $K^+$ enters massively into the hair cells; efflux of this $K^+$ from the hair cells into the outer tunnel of the organ of Corti increases the ionic level in the extracellular fluid. If this $K^+$ is allowed to accumulate in the tunnel fluid, it would cause outer hair cell cytotoxicity. Clearly, $K^+$ recycling from the organ of Corti back to the endolymph or to the stria vascularis plays an important role,

preventing an adverse local effect on the hair cells and allowing $K^+$ ions to be saved.[65] Solvents transit from the outer sulcus into the organ of Corti, where they likely disrupt the role played by the Hensen and Tectal cells, thereby affecting $K^+$ recycling.

**Neuropharmacological effects of solvents—**Nearly a century ago, volatile chemicals were thought to produce non-specific effects on the central nervous system (CNS). More recently, clear evidence has emerged regarding how inhaled solvents act specifically on several types of ion channels expressed in neurons.[66] Many abused inhalants such as toluene may enhance inhibitory synaptic responses through their action on specific sites or through similar mechanisms of action to other CNS depressants, like anesthetics.[67,68] For instance, N-methyl-D-aspartic acid,[69] δ-aminobutyric acid, glycine,[70] adenosyl triphosphate,[71] serotonin,[72] and nicotinic acetylcholine receptors[73] are all involved in CNS function and are sensitive to toluene. Recently, Lataye et al.[74] and Maguin et al.[75] showed that toluene could alter acetylcholine receptors and voltage-dependent $Ca^{2+}$ channels function in *in vivo* studies. Consequently, toluene, like most aromatic solvents, can affect the middle-ear acoustic reflex (the contraction of the middle-ear muscles that occurs in response to high-intensity sound stimuli). This reflex is driven by a cholinergic efferent system.[76] This type of effect suggests that the hearing loss observed in solvent-exposed subjects might be due to dysfunctions beyond the peripheral auditory system, which could at least partially explain the synergistic effects of co-exposure to noise and aromatic solvents.

## Co-exposure

**What is the evidence from animal experiments?:** Experiments with rats have shown that combined exposure to noise and solvents (such as toluene, styrene, and ethylbenzene) induces *synergistic* adverse effects on hearing.[77–81] In most of these investigations, high concentrations of solvents were used for short intervals of time, conditions which do not accurately reflect occupational exposure conditions.

Another difficulty with recreating real-life conditions stems from the fact that humans 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. In studies with experimental animals, researchers have demonstrated that when other stressors are added (such as impact noise or carbon monoxide), or when the animals are active during the chemical exposure, the lowest concentration at which solvents elicited an auditory effect was reduced.[79] Another complication in determining the concentration needed for hearing loss is that workers are often not aware of the concentration to which they are exposed, and many factors can interact to cause effect. However, cases of hearing loss have been observed after exposures that were within permissible European limits, these will be detailed in the next session.

Lataye et al.[79] found interactive effects of noise and styrene with quite low levels of noise: A time-weighted average (TWA) of 85 dB and low concentration of styrene: 400 ppm, 6 h per day, 5 days per week for 4 weeks. In this investigation, solvent absorption was increased by forcing animals to walk in a special wheel during the exposure; as this reflects more closely human exposure scenarios where subjects are rarely stationary.

Recently, it has been reported that some aromatic solvents reduce the protective role played by the middle-ear acoustic reflex.[76] A dysfunction of this reflex would increase risks to hearing by allowing higher acoustic energy levels to penetrate the inner ear.[75,82] This would make co-exposure more dangerous than exposure to noise or to styrene alone.

**What is the evidence from epidemiological studies?:** In general, clinical or epidemiological studies are designed to test hypotheses, such as the hypothesis that certain chemicals are ototoxic. Several clinical and epidemiological studies confirmed an association between exposure to solvents (styrene, toluene, xylenes, solvent mixtures, and jet fuels) in the workplace and increased prevalence of hearing loss, as well as poor hearing thresholds beyond the traditional 4 kHz noise-related audiometric notch.[83–92] For an extensive review of human studies, see Johnson and Morata[93] (available online at https://gupea.ub.gu.se/handle/2077/23240).

To examine dose–response relationships, large populations and detailed exposure information would be needed, which can be very challenging to obtain. Thus, the limitations of existing studies (e.g., study designs, insufficient characterization of the exposure levels for chemicals and noise, and lack of details on whether and how other risk factors were accounted for) do not allow us to identify the following: (1) the type of interaction between the agents and how their results can be used to estimate dose–response relationships or (2) the lowest concentrations necessary for an effect to be detected for the solvents covered in the present document. Overall, studies conducted with experimental animals provide the most robust evidence regarding mechanisms and dose–effect relationships between agents and effects on the auditory function or physiology.

Given the difficulties of extrapolating animal findings and analyzing the data obtained from human studies, those in charge of prevention policy must consider both experimental and epidemiological studies.

The approaches adopted in different countries have been described in two recent reviews.[5,93] Overall, with combined exposure to noise and organic solvents, interactive effects may be observed depending on the parameters of noise (intensity and impulsiveness) and the solvent-exposure concentrations. In case of concomitant exposures, solvents can exacerbate noise-induced impairments even with a noise intensity below the European permissible limit value.

From a mechanistic point of view, solvent-induced hearing impairment in humans would suggest the involvement of both the inner ear and the central nervous system.

## Non-aromatic solvents

### What do animal experiments show?

Trichloroethylene is a cleaning and degreasing agent that can also be used for extractions in different chemical processes. Exposure to high concentrations of trichloroethylene has been shown to disrupt cochlear sensory hair and spiral ganglion cells as well the auditory nerve pathways within the cochlea.[94–98]

In contrast, carbon disulfide (used as a solvent for lipids, sulfur, rubber, phosphorus, oils, resins and waxes), as well as n-hexane (used as a cleaning agent for textiles, furniture, and leather) have been shown to affect the auditory nervous pathway beyond the cochlea in animals[99–103]; for review see Vyskocil et al.[104] These two solvents are associated with retrocochlear dysfunctions.

### Nitriles

Nitriles are mainly used for the preparative synthesis of carboxylic acids. However, acetonitrile is used as a solvent, benzonitrile as an initial compound for melamine resins, and acrylonitrile as a monomer for polyacrylonitrile. The ototoxic effects of these compounds have been demonstrated in animal experiments only. Cis-2-pentenenitrile, 3-butenenitrile, cis-crotononitrile, and 3,3′-iminodipropionitrile were shown to cause cochlear hair cell losses and spiral ganglion cell losses, respectively, in rats, mice, guinea pigs, and frogs.[13,105,53] In contrast, acute exposure to acrylonitrile in rats produces a transient reduction in auditory sensitivity in the high-frequency range.[106]

After administration of acrylonitrile, noise-induced hearing impairment was significantly potentiated in rats.[106] Under test conditions in which neither acrylonitrile nor noise exposures caused any permanent hearing loss, combined exposure caused permanent hearing impairment and significant losses of the outer hair cells. Thus, hearing loss may occur at low noise intensities if simultaneous exposure to acrylonitrile occurs. Pouyatos et al.[107] hypothesized that acrylonitrile increases the risk of noise-induced oxidative damage to the inner ear by impairing the antioxidant's defense mechanisms of the cells.

### Asphyxiants

Carbon monoxide and hydrogen cyanide (salts: cyanides) are two well-known ototoxic asphyxiants. The first is found in exhaust fumes when combustion processes are incomplete in motor vehicles, poorly ventilated stoves and furnaces, acetylene welding, or in enclosed areas (mines and tunnels). Hydrogen cyanide is used as an intermediate product in the organic synthesis of carboxylic acids, pharmaceuticals, dyes and pesticides; relatively large quantities are also required for the surface treatment of metals, galvanizing, and the cyanide leaching process.

**What do animal experiments show?—**The ototoxicity of asphyxiants is believed to be a consequence of effective oxygen deprivation (hypoxia) within the cochlea. In animal experiments, exposure to carbon monoxide or cyanide has reversible auditory effects at low concentrations and impairs cochlear function under severe exposure conditions.[108–110] These experimental studies showed that the two asphyxiants predominantly affect hearing for high-frequency tones, and suggested that while cyanides induce dysfunction of the stria vascularis,[110] carbon monoxide produces excessive glutamate release (glutamatergic excitotoxicity) in the synaptic area below the inner hair cells.[111]

Both carbon monoxide and cyanides have been found to potentiate permanent noise-induced hearing loss in animals and humans.[106,112–118] This potentiation may be the result of a

reduction in the cell's ability to repair noise-induced damage due to carbon monoxide poisoning.[112,113]

**What do epidemiological studies show?—**In a large epidemiological investigation conducted by Lacerda et al.,[118] the hearing thresholds of employees working in noisy occupational environments with combined carbon monoxide exposures were compared with the hearing thresholds of employees working in noisy occupational environments without carbon monoxide. The analysis was based on 9396 audiograms collected by the Quebec National Public Health Institute between 1983 and 1996. The results showed significantly higher hearing thresholds at high frequencies (3, 4 and 6 kHz) for the carbon monoxide-exposed group, with more pronounced effects observed as the duration of exposure increased (15–20 years of exposure).

For an extensive review of human studies with carbon monoxide using other designs, see Johnson and Morata.[93] Even though further human studies are needed to clarify these findings, noise-induced hearing impairment also appears to be potentiated by carbon monoxide in humans.

**Tobacco smoke—**Although a few studies have found no association between smoking and hearing impairment,[119,120] numerous epidemiological studies suggest a link.[121–126] Tobacco smoke contains hydrogen cyanide among other compounds, and results from epidemiological investigations indicate that smokers may have an increased risk of noise-induced hearing impairment.[121,127]

## Metals and metal compounds

**Lead and mercury—**Lead and mercury are metal compounds that are known to be neurotoxic, and therefore ototoxic.[128,129] Lead and lead compounds can be found in the manufacture of lead–acid batteries and plastic, in ship breaking, in paint and petrol. Lead may also be present during car radiator repair, welding, plumbing, smelting, refining, and mining. Mercury can be found in the chlorine–alkali (chloralkali) industry; the industrial process is performed in mercury cells in which mercury acts as the cathode to produce chlorine and sodium hydroxide. Like lead, mercury compounds may be used in batteries (mercuric oxide) and found in pigments, catalysts, explosives (mercury fulminate), laboratory-based research, and in some pharmaceutical applications.

Several studies carried out with monkeys exposed long-term to lead, and epidemiological studies on lead-exposed workers suggest that lead has an ototoxic effect caused by a neurotoxic mechanism.[130–134] Similarly, mercury compounds were shown to induce hearing-damaging effects both in laboratory animals (methyl mercury chloride and mercuric sulfide) and humans.[135–138]

A few studies did not confirm the effect of these metals on hearing,[139,140] but, given the current evidence from human studies, lead and mercury do appear to be ototoxic.

**Tin and organic compounds—**Tri-n-alkyltins are phytotoxic agents used as powerful bactericides and fungicides. Trimethyltin and triethyltin induce hearing impairments in both

rats and guinea pigs, the severity of which is dose-dependent.[141–145] Acute limbic-cerebellar syndrome, which includes hearing impairment and involuntary eye movements (nystagmus), was detected in six industrial workers who inhaled trimethyltin.[146]

**Germanium and manganese—**Germanium and manganese are found in the manufacture of steel alloys, dry-cell batteries, electrical coils, ceramics, matches, glass, dyes, in fertilizers, welding rods, as oxidizing agents, and as animal food additives.

The administration *per os* of germanium dioxide (100 mg/kg/day for 4 weeks and 0.5% in food for 2 months) provoked hearing impairment in rats and guinea pigs due to degeneration of the stria vascularis and the cochlear supporting cells.[147] Other authors assessed alterations of brainstem transmissions in similar tests.[148]

Nikolov[149] reported in 1974 that the potential ototoxicity of manganese may be exacerbated by exposure to noise, and that workers exposed to both manganese and noise seemed to have accelerated hearing impairment compared with those exposed to manganese alone.

### Halogenated hydrocarbons

Finally, there is a strong suspicion for an ototoxic potential of *cadmium* and *arsenic* compounds, as well as *halogenated hydrocarbons* [polychlorinated biphenyls (PCB), tetrabromobisphenol A, hexabromocyclododecane and hexachlorobenzene].[150–152] Animal data suggest that halogenated hydrocarbon-induced hearing impairments are the sequelae of thyroid gland disorders caused by some of these substances.[153,154] In addition, Powers et al.[155] proposed in 2006 that polychlorinated biphenyls could have a direct adverse effect on the outer hair cell function.

## Chemical intoxication and presbycusis

Presbycusis refers to a constellation of age-related physiological degenerations, causing a bilateral loss of hearing sensitivity ranging from high to low audiometric frequencies and a decreased ability to understand speech, particularly in the presence of background noise.[156–158] From a histopathological point of view, four predominant types of presbycusis can be identified[159]:

- *Sensory presbycusis*, which refers to the loss of sensory hair cells and supporting cells in the cochlea.
- *Neural presbycusis*, which refers to degeneration of nerve fibers (Fig. 2) in the cochlea and central neural pathways. A large decrease occurs in the density of spiral ganglion cells and afferent fibers, especially evident in the apical turn of the spiral ganglion (Fig. 6, bottom panels).
- *Strial presbycusis*, which results from degeneration of the stria vascularis in the cochlea. Strial presbycusis is characterized by vascular stenosis and reduced vascularization.
- *Mechanical presbycusis*, which results from morphological changes of the basilar membrane of the cochlea.

At younger ages (<50 years), the first effects of presbycusis are normally concealed by central counterbalancing mechanisms. Indeed, after an acoustic trauma or an ototoxic intoxication, the central nervous system can increase the spontaneous firing rate of neurons in the dorsal cochlear nucleus[160,161] or decrease gabanergic inhibition in the inferior colliculus.[162,163] This neural hyperactivity maintains a suitable level of excitability of the auditory nerve cells: the phenomena are called “up-regulation” in the dorsal cochlear nucleus and “down-regulation” in the inferior colliculus. In addition to these up- and down-regulations within the auditory central nuclei, younger subjects have more cochlear hair cells than necessary for assuring normal hearing. As a result, a limited loss of hair cells can be sustained without leading to significant hearing deficits.[164] For all these reasons, the effects of ototoxic substances in an exposed population cannot be fully determined by pure-tone audiology (PTA) alone.

## What are the consequences of trauma or poisoning on the first manifestations of presbycusis?

Noise exposure (even at moderate intensity) or chemical intoxication can exacerbate age-related hearing loss and lead to early presbycusis, due to exhaustion of the compensatory strategies developed by the different features of the hearing system.[165] Like noise, the effects of ototoxic agents are insidious and hard to correlate with the duration of exposure. Hearing damage is generally identified after several years of exposure when it is too late to take preventive action. An early diagnosis of presbycusis is definitely an admission of failure. Preventive action must be taken when it is still possible to preserve workers’ hearing. As a result, we believe PTA is not the appropriate test to use for auditory follow-up when people are exposed to noise or ototoxic agents.

Although many people experience a decrease in hearing acuity with age, others do not, and it is not possible to predict who will and who will not develop hearing loss as they get older. The median hearing loss attributable to aging for a given age group cannot be generalized to all individuals in that age group. Thus, when calculating significant threshold shifts, age-correcting hearing thresholds will overestimate the expected hearing loss for some people and underestimate it for others.

The adjustment of audiometric thresholds to account for age-related effects has become a common practice in workers’ compensation litigation. The age-correction of audiograms measured as part of an occupational hearing loss prevention program is not recommended.[166]

## Patient evaluation, diagnosis, prevention and treatment

Today, few health care providers inquire about hearing loss. In fact, among older adults, 60 years of age and older, only 15% of the primary care providers asked or screened patients for hearing loss.[167] If hearing loss is rarely addressed among older adults, for whom many providers would expect hearing loss to be an issue, even fewer clinicians are likely to inquire about hearing loss and tinnitus among middle-aged persons who are exposed to ototoxic substance and/or loud noise in the work or home environment (hearing risks are not confined solely to workplace noise or chemical exposures). Each case history should

investigate risk factors in all aspects of the subject's daily activities, including occupational and nonoccupational tasks, and be followed by appropriate referral and/or counseling. In addition, if hearing is found to be impaired (regardless of etiology), this should not dissuade the physician from encouraging the patient to protect their residual hearing. Each consultation offers a chance for education that should not be wasted. Subjects who are at risk of hearing loss and tinnitus due to exposure to ototoxic substances and noise need to be fully informed about the risks they run and the protection strategies that can be implemented. They must assume responsibility for using personal protective equipment, and develop the habit of using it whenever they are exposed to loud noise (both on and off the job). Thus it is important for health professionals to make a point of seeking out risks to patients' hearing and advising them appropriately. Many resources are available to help guide counseling activities, including online materials from professional organizations, advocacy groups, government agencies, and vendors of hearing-related health products. However, as the accuracy of information varies greatly among online resources a critical review should be undertaken before using the information.

## Evaluation and diagnosis

Dysfunctions of the central auditory nervous system following occupational exposures have been described on the basis of results from behavioral tests, despite some studies reporting normal hearing thresholds.[168–173] This suggests that hearing loss caused by chemicals can affect a worker's life more extensively than noise-induced hearing loss, because sounds are perceived not only as less loud, but also as distorted. Word recognition may also be compromised.

While pure-tone air-conduction audiometry (PTA) remains the most commonly used clinical test both in the United States and Europe to measure the extent of temporary and permanent hearing loss, it has been shown to be insufficient for examining hearing loss from mixed exposure to noise and ototoxic agents, because it does not allow the source of the problem to be diagnosed (i.e., cochlear *vs.* retrocochlear). In the case of central hearing loss, a PTA can indicate normal hearing, but a person can still have difficulty understanding speech, particularly in background noise, making it difficult to hold a conversation in a busy restaurant or at a party. Thus, for persons exposed to ototoxic chemicals in isolation or in combination with noise it is important to use tests that evaluate the auditory system more comprehensively, from the cochlea to the higher auditory pathways. These tests may help differentiate between the individual (or the combined) effects of noise and ototoxicants on hearing.

As a result, PTA should be complemented with supplementary prevention tools such as distortion product otoacoustic emissions (DPOAEs). Cubic DPOAEs detect inner-ear dysfunctions only, particularly those involving the outer hair cells sensitive to noise and ototoxicants. The inclusion of DPOAEs in a battery of tests to assess hearing would facilitate the distinction between sensory and neural hearing disorders. By combining DPOAE measurements with contra-lateral acoustic stimulation, the stapedial reflex can also be measured. This is important as ototoxicants were recently shown to affect the central nuclei driving the middle-ear acoustic reflex.[76,82] Therefore, from a safety point of view, it

would be more efficient to collect and measure performances both in the middle ear and in the inner ear. The acoustic reflex would allow chemically induced retrocochlear disorders to be evaluated. Equipment is being designed to offer an alternative to subjective PTA to detect early-stage hearing impairment. One example is the EchoScan, which can provide sensitive, objective, quick, and reliable measurements of both inner- and middle-ear performances, taking both the age and gender of subjects into account.[174] This system does not require stringent acoustic conditions (it does not have to be carried out in a sound-proof booth, it can be carried out in a quiet room), making it very convenient for use in the workplace. It is therefore suitable for occupational medicine, especially for the auditory follow-up of people exposed to noise and/or ototoxic agents. The major advantage of EchoScan is that it facilitates detection of the middle-ear reflex, which is quite sensitive to the neuropharmacological effects of some ototoxic substances. As a result, EchoScan can assess both the inner-ear (amplitude of the distortion products) and the middle-ear reflex at the end of a working day. Fifteen minutes before and after the exposure are enough to go through all the tests and to obtain an idea of the cochlear and retrocochlear effects of suspected substances. This system is quite promising for early detection of effects in hearing conservation programs.

Although ideal, we acknowledge that the routine use of an extensive battery of audiological tests in primary care settings may be prohibitive because of time and cost constraints. In the face of such constraints, the selection of a minimum battery of tests with proven validity and reliability, as well as availability and ease of administration, becomes crucial for planning a protocol for routine evaluation.

### Prevention

While hearing loss is one of the principal work-related disabilities among various groups of workers, a considerable number of losses could be prevented if exposure to known oto-toxic chemicals, alone or in combination with even mild to moderate noise, was included in risk assessment and management. The initial steps of hearing loss prevention programs are hazard assessment and control. It is important to learn whether and which hazardous exposures exist in a workplace. 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 interventions are required by law. The most effective way to prevent hearing loss due to noise or chemical exposure is to remove the source of risk from the workplace by engineering controls, finding alternatives to minimize exposure (such as reducing the duration of exposure), or requiring the use of personal protective equipment if engineering or administrative controls do not eliminate exposure. If the use of personal protective equipment is required, it should be worn as directed. Many professional organizations and government agencies have comprehensive sources of information to help guide your counseling activities.

## Conclusions

Evidence of how hearing dysfunctions can be caused by chemicals and the combined effects of co-exposures to noise and ototoxic chemicals have emerged predominantly from animal

tests in which these associations have been demonstrated. Animal studies have been used to assess the specific effects of several substances to be studied in controlled and appropriate experimental conditions. These findings are supported by cross-sectional epidemiological studies in workers from different industrial sectors exposed to styrene, toluene, solvent mixtures, carbon disulfide, or to a combination of noise and solvents such as toluene, styrene, and ethylbenzene. The risks encountered by workers exposed to chemicals or to chemicals and noise are real, and data obtained from animal models must not be neglected. Today, our scientific knowledge is robust enough to recommend at least precautionary measures for use in occupational environments where workers are exposed to chemicals.

## Recommendations

Recognizing the risk of occupational chemical exposure on hearing, the European noise legislation (Directive 2003/10 EC noise)[175] as well as the U.S. Army Hearing Conservation guidelines already included ototoxic chemical exposure as a risk factor to be considered in risk assessment and prevention strategies for hearing. The U.S. Army Center for Health Promotion and Preventive Medicine[176] also issued a recommendation to consider ototoxic chemical exposures for inclusion in a hearing conservation program and to provide annual audiograms for workers exposed to these chemicals, particularly in combination with marginal noise. The American College of Occupational and Environmental Medicine (ACOEM) guidance statement also indicates that exposure to ototoxicants should be considered when health professionals evaluate sensorineural hearing loss (ACOEM, 2012).[177]

The American Conference of Governmental Industrial Hygienists (ACGIH) stated in its Threshold Limited Values® and Biological Exposure Indices® publications that periodic audiograms are advised and should be carefully reviewed in occupational settings where exposure to toluene, lead, manganese, or n-butyl alcohol occurs.[178] But none of these require clear hearing controls following exposure to ototoxic substances or to co-exposures with noise. In fact, no regulations require workers' hearing to be monitored when they are exposed to ototoxic chemicals. Tests for ototoxicity should be standardized and incorporated into national, or even international guidelines. More frequent medical monitoring should be considered for workers exposed to ototoxic substances, irrespective of the noise exposure level, and workers' health results should be recorded to allow early changes at individual and collective levels to be detected.

The audiological control of workers exposed to noise, chemicals, or both should go further than PTA or DPOAE measurements to take the main dimensions of hearing impairments into consideration. An assessment of the loss of communication skills, a middle-ear test (a quick measure of the stapedial reflex), and questionnaires on therapeutic treatments or exposure to chemicals should be included in the battery of audiological tests used to allow early detection and correctly evaluate the total effects on workers hearing. This battery of tests could also be used as an early indicator of neurotoxicity and would be helpful to evaluate the toxicity of industrial chemicals and establish occupational exposure limits.

Ideally, after hospitalization and before returning to work, employees should be interviewed by an occupational physician and potentially ototoxic drugs administered as part of the treatment should be listed. Because the precautionary principle of the EU Commission requires an adequate level of protection even when scientific data are insufficient or ambiguous, individual hearing protectors are recommended for at least 3 months post-treatment for exposures of 80 dBA and above (time-weighted average) in a complex occupational environment (noise plus chemical ototoxic substances). (The precautionary principle is based on evidence that is graded as fair and information from one or two studies that are judged to be reliable.) A special label for ototoxic substances may be considered for chemicals.

For too long, hearing loss prevention has been viewed as a specialized area for a few professionals who manage occupational hearing conservation programs. Hearing loss due to work-related exposure represents a substantial portion of all hearing impairments. Because most work-related hearing losses are permanent, the only way to reduce their burden on society is to prevent them. Without intervention, the financial and social costs of hearing loss also become significant. Physicians have the tools and the opportunity and are in a strategic position to advocate for healthy hearing practices and to facilitate hearing loss prevention. The public health nature of work-related hearing loss and the magnitude of the problem in today's society require their increased involvement.

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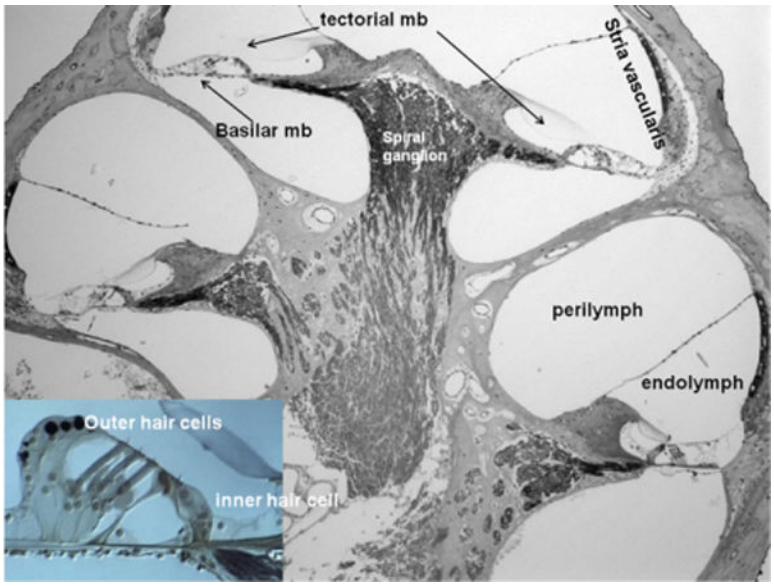


**Fig. 1.**

Cross section of the cochlea. mb, membrane. Left bottom panel: organ of Corti. (Color version of the figure is available online.)

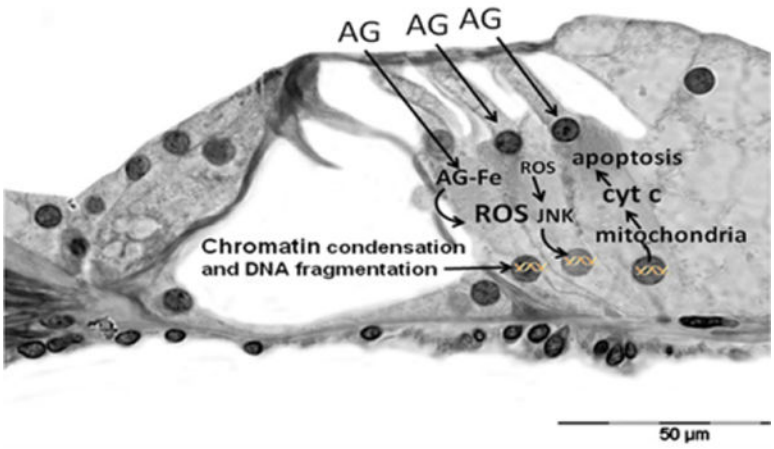


**Fig. 2.**

Mechanisms of aminoglycoside-induced outer hair cell damage. AG, aminoglycoside; AG–Fe, aminoglycoside– iron complex; ROS, reactive oxygen species; JNK, c-Jun N-terminal kinase; Cyt C, cytochrome C. Adapted from Rybak and Ramkumar.[21]

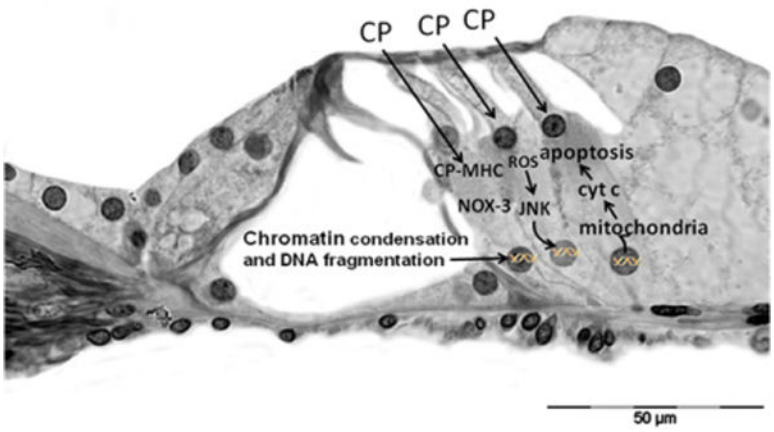


**Fig. 3.**

Mechanisms of anticancer drug toxicity. CP, cisplatin; MHC, monohydrate complex; ROS, reactive oxygen species; NOX-3, NADPH oxidase 3; Cyt C, cytochrome C. Adapted from Rybak and Ramkumar.[21]

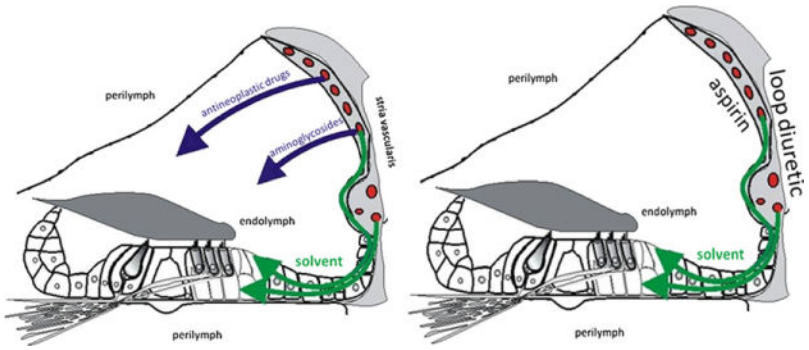


**Fig. 4.**

Intoxication route for different medicines and work-related substances. (A) Anti-neoplastic drugs and aminoglycosides are hydrophilic substances, whereas solvents are lipophilic substances. (B) Loop diuretics modify the activity of the ionic pumps, whereas aspirin affects blood fluidity within the stria vascularis. As a result, the ionic concentration of endolymph is disturbed until the molecules are cleared from the system. (Color version of the figure is available online.)

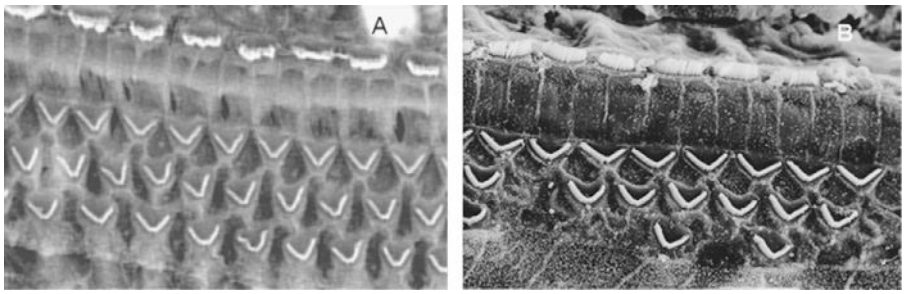


**Fig. 5.**

Scanning electron micrograph of a rat organ of Corti prior to- (A) and post- (B) toluene exposure. When present, the stereocilia of the hair cells look normal in both images.

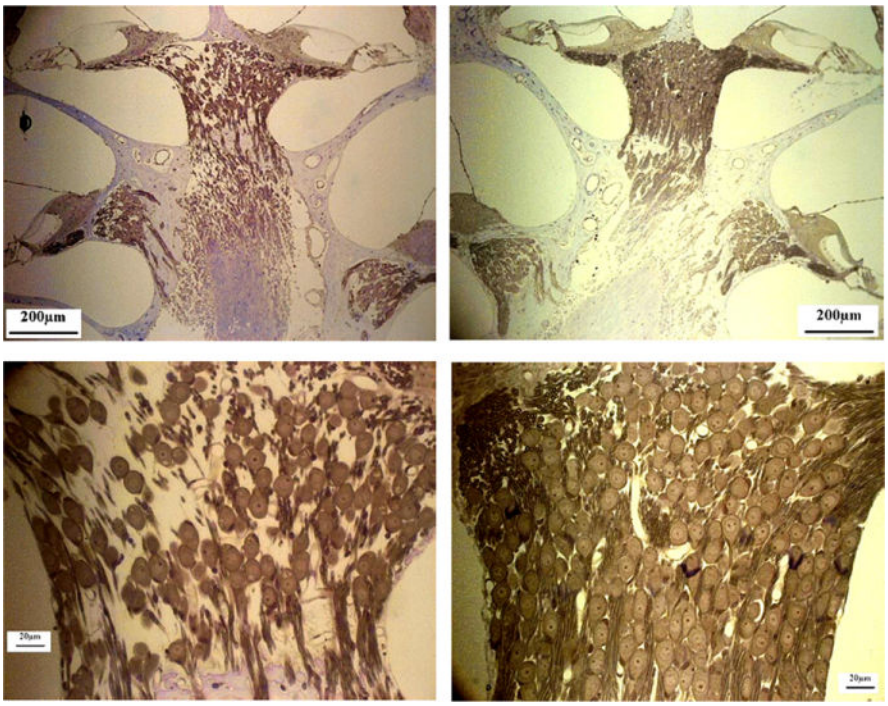


**Fig. 6.**

Neural presbycusis. Mid-modular cut cochlea. The left panels correspond to a 25-month-old rat, whereas the right panels correspond to a 5-month-old rat. (Color version of the figure is available online.)