

# Exposure to ototoxic agents and noise in workplace – a literature review

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## ABSTRACT

Occupational noise and its impact on worker's hearing is very well investigated, managed and regulated in Australia. Depending on the duration of noise exposure, its characteristics and levels, occupational noise can be a source of annoyance, fatigue and hypertension. Additionally, noise causes significant irreversible hearing damage. Ototoxic chemicals in the workplace also affect our hearing and synergistically exacerbate hearing loss when workers are also exposed to a noisy workplace environment. This paper will review literature on several, major ototoxic agents that are commonly used across industries in Australia; the proposed mechanism of hearing loss due to ototoxicity; the limits of exposure; synergistic effect of noise exposure and ototoxic agents; the strategy of noise survey in ototoxic-noise exposure; available control measures; exposure standards; and the need for further knowledge. This paper aims to assist Workplace Health and Safety (WHS) professionals in identifying the potential ototoxic hazards in their workplace and organise hazard management plans to minimise the potential health risk and injury to the workers hearing.

## 1. INTRODUCTION

Occupational Noise-Induced Hearing Loss (ONIHL) is a key concern for workplace health and safety and identified as a significant health and economic problem in Australia (Safe Work Australia, 2010). Noise generated by equipment, machinery or an industrial process is a physical factor that causes mechanical and metabolic damage to the hearing system including the peripheral auditory receptor, the cochlea, and more rarely, to the auditory neural pathways (Campo et al., 2013). In addition to the physical noise as a contributing factor, accumulated evidence in recent years demonstrates that occupational hearing loss can be exacerbated by exposure to some organic solvents (e.g. toluene and styrene), asphyxiants (e.g. carbon monoxide), heavy metals (e.g. lead and mercury), pesticides and herbicides (e.g. organophosphates and paraquat) which are widely used across many industries (Campo et al., 2013, Choi et al., 2014, Eberhard, 2012). Ototoxic substances are absorbed into the bloodstream and may affect the structures and/or the function of the inner ear and the connected neurological pathways (EU-OSHA, 2009; Safe Work Australia, 2011). The European Agency for Safety and Health at Work (EU-OSHA, 2009) defines ototoxic agents as all substances that may affect the structures and/or the function of the inner ear (auditory plus vestibular apparatus) and the connected neural pathways. "Ototoxicity" refers to toxic damage to the sensory or secretory epithelia of the labyrinth and the auditory nerve, i.e. the pathology within the temporal bone. There has been increased research interest in recent years on the combined exposure to noise and ototoxic agents in the workplace and its impact on hearing. The European Agency for Safety and Health at Work (EU-OSHA, 2009) recognises this as an "Emerging Risk" at the workplace.

## 2. OTOTOXIC AGENTS COMMONLY USED IN INDUSTRY

The key audiological symptom of ototoxicity is poorer hearing thresholds than expected relative to age (Morata et al., 1993). Median baseline values for age-related hearing thresholds are available in ISO 7029 and a section is reproduced here in Figure 2 for reference. Threshold shifts produced by the ototoxic agents may compound those produced by excessive noise exposure alone (AS/NZS 1269.0:2005). Campo et al. (2013) noted that several clinical and epidemiological studies confirmed an association between exposure to several ototoxic agents in the workplace and increased prevalence of hearing loss, as well as poor hearing thresholds beyond the traditional 4 kHz noise-related audiometric notch. It is currently thought that there are more than 700 different groups of chemicals that are ototoxic in nature, however, only a limited number of chemicals have been investigated for their association with hearing loss. Substances that have been found to have potential ototoxic effects in the workplace are generally

classified into three major classes namely Solvents, Heavy Metals and Asphyxiants & Others (Fuente et al., 2012; Safe Work Australia, 2011). These are discussed in the following sections.

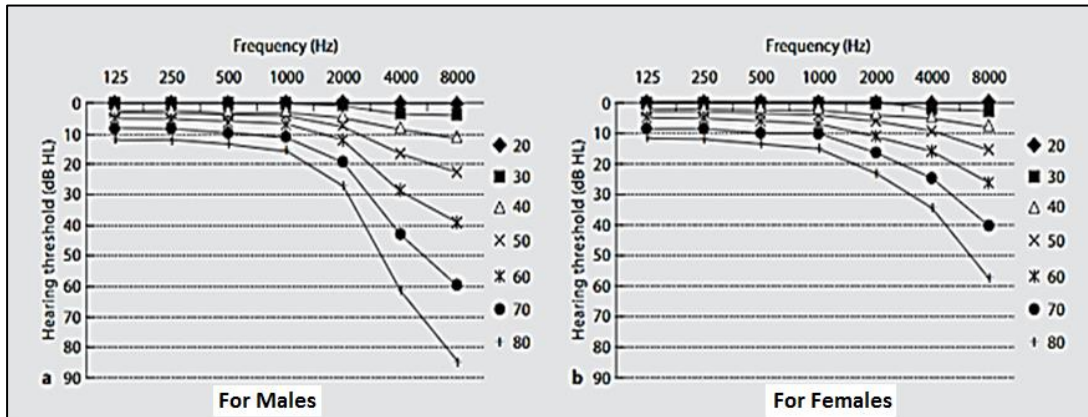


Figure 2: Hearing thresholds for different age and gender group (ISO 7029)

### 2.1 Solvents

Occupational hearing loss due to exposure to solvents is often known solvent-induced hearing loss (SIHL). Some of the key solvents and their industrial use are listed in Table 1 (Fuente et al., 2012; Safe Work Australia, 2011; Nies, 2012; Hodgkinson et al., 2006; Toppila, 2010). Studies show that hearing loss due to exposure to ototoxic solvents can affect the inner ear, peripheral and central auditory pathways. Hearing losses generally occurs in the high frequency region but may often affect a wider range of frequencies of human hearing. Epidemiological studies in humans show that exposure to ototoxic solvents affects cochlear hair cells and can aggravate irreversible hearing impairment (Hodgkinson et al., 2006).

Table 1. Commonly used organic solvents that are ototoxic in nature

Organic solvent	Industrial uses/ Exposure
Toluene	Electroplating, adhesive manufacture, laboratory chemicals, metal degreasing, paint manufacture, paint stripping, paper coating, pharmaceuticals manufacture, printing, rubber manufacture, wood stains and varnishes, and footwear manufacture.
Styrene	Fabrication of fibreglass boats, pulp and paper manufacture and in plastics, resins, coatings, and paint manufacture.
Xylene	Laboratory chemicals, machinery manufacture and repair, paint manufacture, paint stripping, paper coating, pesticide manufacture, pharmaceuticals manufacture, printing, rubber manufacture, and in wood stains and varnishes.
Ethyl benzene	Machinery manufacture and repair, paint manufacture, paper coating, rubber manufacture, wood stains and varnishes.
Trichloroethylene	Electroplating, integrated iron and steel manufacture, machinery manufacture and repair, metal degreasing, pulp and paper manufacture.
Carbon disulphide	Extraction processes, grain fumigant, manufacturing process for rayon and cellophane
Ethanol	Transport Fuel, Biofuels,
n-heptane	Printing, Solvent in Laboratory, Quick dry glossy paints and glue, varnishes and inks
n-hexane	Textile cleaning agent, Furniture and leather industry, Laboratory, Fuel Industry, Paint dilution,

### 2.2 Heavy Metals

Several heavy metals have been identified as ototoxic and found to impair inner ear cells, leading to auditory function disorders. Table 2 summarises the industrial uses of some common ototoxic heavy metals (EU-OSHA, 2009; Fuente et al., 2012; Safe Work Australia, 2011; Nies, 2012). It is evident from epidemiological studies in humans, high levels of heavy metal in blood are often associated with hearing loss. Clinical research and investigations show that

heavy metals usually target an organ or structure, therefore the configuration is characteristic to the area of damage. Heavy metals or compounds have also been found to be related to deafness among other symptoms (Gopal, 2008, Hoeffding et al., 1991). Hearing impairment has been observed in children living in an area heavily contaminated with arsenic (EU-OSHA, 2009).

Table 2. Commonly used heavy metals that are ototoxic in nature

Metal	Industrial uses/ Exposure
Copper	Power generation and transmission of electricity, electrical wires, roofing and plumbing, and industrial machinery.
Lead	Car batteries, ballast keel of sailboats and scuba diving weight belts, soldering and as electrodes in the process of electrolysis, polyvinyl chloride (PVC) plastic that covers electrical cords
Mercury	Manufacture of industrial chemicals, electronic applications, cosmetics, manufacturing of thermometers and fluorescent lamps, medical applications such as dental amalgams.
Zinc	Galvanization, manufacturing of batteries, in copper-base alloys. Manufacture of zinc sheets to be used for sheathing or roofing.
Lithium	Manufacture of batteries, ceramics, glass and pharmaceuticals. In rubber and thermoplastics industries, air treatment and in primary aluminium production.
Arsenic	Production of pesticides, semiconductors, paint, electroplating
Manganese	Manufacturer of steel alloys, dry cell batteries, electrical coils, ceramics, glass, dyes, fertilizers, welding rods, as oxidizing agents, animal food additives

### 2.3 Asphyxiants and Others

The ototoxicity of Asphyxiants such as carbon monoxide and hydrogen cyanide is found to be a consequence of effective oxygen deprivation (hypoxia) within the cochlea (EU-OSHA, 2009).

Table 3. Commonly used asphyxiants and pesticides that are ototoxic in nature

Asphyxiants/Others	Industrial uses/ Exposure
Carbon Monoxide	Exhaust fume in Motor Vehicles, poorly ventilated stoves and furnaces, acetylene welding, or in enclosed areas (mines and tunnels)
Hydrogen Cyanide and its salts	Used as an intermediate product in the organic synthesis of carboxylic acids, pharmaceuticals, dyes and pesticides
Acrylonitrile	Mainly used for preparative synthesis of carboxylic acids, pharmaceuticals
Organophosphates, Paraquat	Pesticides, Agriculture industry

Asphyxiants disrupt intrinsic anti-oxidant defences and make the ear more vulnerable when exposed to noise (Morata, 2012). Pesticides have been found to be associated with poorer hearing thresholds as well as with poorer performance for central auditory functioning (Fuente et al., 2012). Some nitriles such as Acrylonitrile are known to induce vestibular dysfunction and loss of vestibular hair cells (EU-OSHA, 2009). Table 3 summarises the industrial uses of some common ototoxic Asphyxiants, Pesticides and Nitriles (EU-OSHA, 2009; Fuente et al., 2012; Safe Work Australia, 2011; Nies, 2012; Campo et al., 2013).

There are three comprehensive literature studies available which investigated the different ototoxic agents in workplaces and their level of influence or confirmed effect on hearing. The studies were carried out by 1) Canadian Institut de Recherche Robert-Sauvé en santé et en sécurité du travail (IRSST), 2) European Agency for Safety and Health at Work (EU-OSHA) and 3) US National Institute for Occupational Safety and Health (NIOSH) and the Nordic Expert Group (NEG) (Nies, 2012). The ototoxic agents identified in these studies (Toluene, Styrene, Trichloroethylene, Mercury, Lead, Carbon disulfide and Carbon monoxide) are based on sufficient scientific evidence of relevant ototoxic properties (Nies, 2012). Overall, the findings are in very good agreement except for Mercury and Carbon Monoxide which is confirmed by both NEG and EU-OSHA but found non-conclusive and lack of evidence by IRSST. However, the European statistics on occupational diseases and their prevalent causes clearly indicate that ototoxic substances should not divert risk managers' attention from the fundamental requirements in combating noise-induced hearing loss at the workplace that still has priority over chemically induced hearing impairment (Nies, 2012).

### 3. SYNERGISTIC EFFECT OF NOISE EXPOSURE AND OTOTOXIC AGENTS ON HEARING LOSS

Exposures to ototoxic substances and noise have shown adverse interactive effects on hearing which could be additive or synergistic. This interaction can be classified into three categories. Firstly, “additive” interaction in which the effect of a combination of agents is that expected from their dose-response relationship. Secondly, “antagonism” is when the effect is less than expected from the dose-response relationship. Thirdly, “synergism” is when it is greater (EU-OSHA, 2009, Berenbaum, 1989; Calabrese, 1991; Greco et al. 1992; Niall, 1998).

Synergism is further divided into Coalism, Potentiation and Co-synergism. Coalism is where the agents alone are without effect but together produce an effect greater than that seen in controls. Potentiation is where only one agent influences its own but together a greater effect occurs than the dose-response relationship would suggest. Co-synergism is where each agent influences its own but where the combined effect is greater than that expected from dose-response relationship (EU-OSHA, 2009).

Industrial ototoxic agents have been investigated in humans through numerous epidemiologic studies, the findings of which are supported by many studies on animals. Robust evidence from epidemiological studies and research investigations over the last two decades has confirmed that combined exposure to noise and ototoxic substances can aggravate the hearing loss (Campo et al., 2013). The studies on co-exposure of noise and ototoxic agents on hearing loss are summarized below.

#### 3.1 Noise and Ototoxic Solvents

- A 20-year (1958-1986) longitudinal study was performed on 319 Swedish employees from different industrial sectors. The findings showed that despite their lower noise exposure level (compared to the other division), 23% of the employees working in a chemical division suffered from hearing impairment (Barnstorm et al., 1986).
- Several clinical and epidemiological studies confirmed the 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 (Johnson et al., 2010).
- An investigation of workers exposed to styrene found that high frequency hearing loss was experienced by both noise exposed and non-noise exposed groups such that even if workers were exposed to styrene alone, their upper limit of hearing was reduced (Morioka et al., 2000).
- A review of human and animal studies concluded that ethylbenzene, styrene, toluene and trichloroethylene are ototoxic in nature when the workers are co-exposed with noise. Additionally, it was also found that carbon disulfide, n-hexane and xylene are possibly ototoxic at conceivable concentrations in the workplace with exposure to noise (IRSST, 2012)
- A cross-sectional study of plant workers from Sweden, Finland, and Poland with simultaneous exposure to toluene (100 to 365 ppm (parts per million)) and noise (88-98 dB(A)) found significant increase in the predicted probability of developing hearing loss compared to a group of workers exposed to comparable noise levels. (Fuente et al., 2012). In general terms, 1 ppm is equivalent to 1 milligram of something per liter of water (mg/l).
- A recent study in Korea involved 30,072 workers nationwide across a range of industries exposed to noise, heavy metals, and different organic solvents (styrene, n-hexane, and toluene) (Choi et al., 2014). Findings of the research investigations showed that co-exposure to organic solvents and heavy metals may increase the risk of hearing loss due to noise exposure. The findings suggest that the risk of noise-induced hearing loss may vary by industry. Furthermore, employees in industries dealing with heavy metals and/or organic solvents are susceptible to such risks, and these industries should prioritize noise and chemicals reduction to prevent work-related hearing loss.
- Interactive effects of noise are observed at a relatively low sound pressure level of 85 dBA and a styrene exposure concentration of 400 ppm (Fuente et al., 2012).

- Results from recent studies on workers simultaneously exposed to up to 45 ppm toluene and 82 dB noise shows that the threshold for developing hearing loss due to toluene exposure could be above 50 ppm (IRSST, 2012).
- The effects of simultaneous exposure to noise and carbon disulfide were explored in two groups of workers in a rayon factory in Brazil. Research investigations showed that 12.7% of workers exposed to carbon disulfide had hearing losses affected at both higher and lower frequencies compared with 3.5% of workers exposed to noise alone. Hearing losses increased with exposure time to carbon disulfide and noise and could be observed after 3 years of simultaneous exposure (Morata et al., 1989).
- Based on a good amount of literature review, Sulkowski (2010) concluded that a synergistic effect is noted in workers in occupational environments for a co-exposure to noise and carbon disulfide which exacerbates the noise-induced hearing impairment.

### 3.2 Noise and Heavy Metals

- Epidemiological studies on lead-exposed workers suggest that lead has an ototoxic effect caused by a neurotoxic mechanism. Mercury compounds were shown to induce hearing-damaging effects (methyl mercury chloride and mercuric sulfide) on humans. Ototoxicity of manganese was found to be exacerbated by exposure to noise and that workers exposed at co-exposure were found to have accelerated hearing impairment compared with those exposed to manganese alone (Campo et al., 2013).
- Research has shown that exposures to solvents such as toluene and styrene and metals such as lead and mercury can cause hearing loss and, that when there is combined solvent-noise or metal-noise exposures, the risk of hearing loss is higher than for exposures to the agents alone (Johnson and Morata, 2010).
- A recent study on 412 Steel Plant workers in Taiwan revealed a significant association between a relatively low level of lead in the blood (around 7µg/dL or above) and the noise-induced hearing loss at various sound frequencies. The largest impact was found at the high frequencies of hearing loss, especially 6 kHz. Lead exposure may contribute to hearing loss via impairing the auditory nerve conduction and/or the protective function of the outer hair cells, which, in turn, directly exposes the inner hair cells to the less attenuated sound levels (Hwang, 2009).

### 3.3 Noise and Carbon Monoxide

- A large epidemiological investigation was carried out by the Quebec National Public Health Institute between 1983 and 1996 for workers exposed to noise alone and combined exposure to noise and carbon monoxide. The analysis was based on 9396 audiograms. Research findings showed significantly higher hearing thresholds at high frequencies (3 kHz, 4 kHz 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) (Lacerda et al, 2005).

## 4. EXPOSURE STANDARDS FOR COMBINED EXPOSURE TO NOISE AND OTOTOXIC AGENTS

Workers in a workplace environment may be exposed to noise and ototoxic chemicals either in isolation or in combination. Effects of occupational noise on hearing are well investigated and therefore occupational noise exposure standards are generally well established. However, unlike noise exposure, exposure standards for ototoxic agents do not consider the adverse effects of chemicals on human hearing in many countries in the world. This is because human exposure-response relationships remain unclear and therefore chemical exposure standards have not been modified to reduce the risk of hearing impairment (Fuente et al., 2012). The different occupations that are exposed to both noise and ototoxic substances in their workplace and hence subjected to exacerbated hearing damage include: Aircraft maintenance workers, Printing industry workers, Painters, Dry cleaners, Boat builders, Construction Workers, Metal Manufacturer, Leather Manufacturer, Petroleum products manufacturer, Defence (Weapons Firing) workers, Furniture makers, Vehicles/Aircraft re-fuellers, Fire fighters, Fire arm instructors and Agriculture workers/Farmers (Campo et al., 2013; AIOH Position Paper, 2016).

Safe Work Australia's Hazardous Substances Information System (HSIS) provides the exposure standards for different hazardous substances (<http://hsis.safeworkaustralia.gov.au/>) including some that are ototoxic. As the

Material Safety Data Sheets (MSDS) generally do not provide information on ototoxicity (AIOH, 2016), different occupations highlighted in this paper and the different industries where ototoxic agents are commonly used listed in Table 1 to Table 3 should be considered in relation to occupation hearing loss prevention and management.

The interaction between noise and ototoxic agents and their combined effects on hearing is complex. In a real-life workplace setting, workers might often be exposed to noise and a mixture of different hazardous ototoxic agent which makes it difficult to investigate the influence of a single ototoxic agent with noise on hearing (EU-OSHA, 2009). Many of the current epidemiological studies on humans are often limited due to insufficient characterization of the exposure levels for chemicals and noise, and lack of details on whether and how other risk factors were accounted for. Thus, the findings often do not allow identifying the type of interaction between noise and ototoxic agents, how their results can be used to estimate the dose–response relationships and the lowest concentrations necessary for an effect to be detected for the ototoxic agents (Campo et al., 2013).

However, to consider the combined effect of noise exposure and ototoxic agent on hearing loss, many countries have adopted different administrative approaches where workers are exposed to such occupational environments. The Australian Model Code of Practice for Managing Noise and Preventing Hearing Loss at Work (Safe Work Australia, 2011) states that the daily noise exposure of workers exposed to ototoxic agents should be reduced to a maximum A-weighted level of 80 dB. Additionally, it also states that regular audiometric testing is recommended for workers who are exposed to ototoxic substances with airborne exposure more than 50% of the Australian national exposure standards regardless of noise exposure level. In cases where workers are exposed to an 8-hour noise exposure level greater than 80 dBA (Leq) and/or C-weighted peak noise level  $L_c$ , peak greater than 135 dB with any level of ototoxic chemical exposure – audiometric testing should be carried out on a regular basis. The American Conference of Industrial Governmental Hygienists recommends that periodic audiometry should be carried out and the results should be carefully reviewed for combined exposure (Fuente et al., 2012). The United States Army also recommends annual audiometric testing when chemical exposure (disregarding the use of respiratory protection) is equal to or greater than 50% of the most stringent criteria for occupational exposure limits, regardless of the noise level (Fuente et al., 2012). Scientists from INRS in France recommended lowering exposure limit of styrene from 50 to 30 ppm (TWA) in addition to the compulsory use of hearing protectors for 8-hour noise exposure levels above 80 dB(A) (EU-OSHA, 2009). The EU Noise Directive 2003/10/EC requires the employer to assess the occupational risk not only from exposure to noise at work but also to the combined exposure to noise and occupational ototoxic compounds (EU-OSHA, 2009). As combined exposure to noise and ototoxic agents are not considered yet in establishing the occupational exposure levels for chemicals, a “noise notation” proposed by Hoet and Lison (2008) has been adopted by Sweden, France and Switzerland to indicate an increased risk of hearing loss in combined exposures.

## 5. MECHANISM OF HEARING LOSS AT COMBINED EXPOSURE

There are two specific mechanism associated with ONIHL - Mechanical and Metabolic Mechanism. Mechanical damage is often found related to the characteristics of the noise such as impulsiveness and its amplitude. In this mechanism, stress is developed at the Organ of Corti exceeding the elastic limits of the tissues, causing hearing damage (EU-OSHA, 2009). Mechanical mechanism is dominant generally at higher noise levels. In contrast, metabolic mechanism is found associated with the prolonged exposure to noise and generally dominant at lower noise levels. In metabolic mechanism, the reactive oxygen metabolites (ROM) and other highly reactive endogenous substances play a significant role in NIHL (EU-OSHA, 2009).

Ototoxic chemicals can enter our body through inhalation, skin absorption and ingestions (AIOH, 2016). Interactive effects may occur with co-exposure to noise and ototoxic agents, depending on the parameters of noise (level and impulsiveness) and the ototoxic agents' exposure concentrations (Campo et al., 2013, AIOH, 2016). In case of concomitant exposures, hearing impairment in humans involve both the inner ear and the central nervous system (Campo et al., 2013). Noise exposures predominantly damage the cochlea and the peripheral auditory system while ototoxic agents damage both the cochlear structures and the central auditory system. Refer to Figure 1 for an illustration on human auditory system. Ototoxic agents cause degeneration of hair cells and the auditory pathway and/or auditory cortex may also be affected. The damage in the cochlea is caused by the formation of the reactive oxygen metabolites (ROM) (Toppila, 2010; Sulkowski, 2010). Reduced blood flow and free radical formation are important ototoxic mechanisms shared by noise and chemical exposures (Morata, 2012).

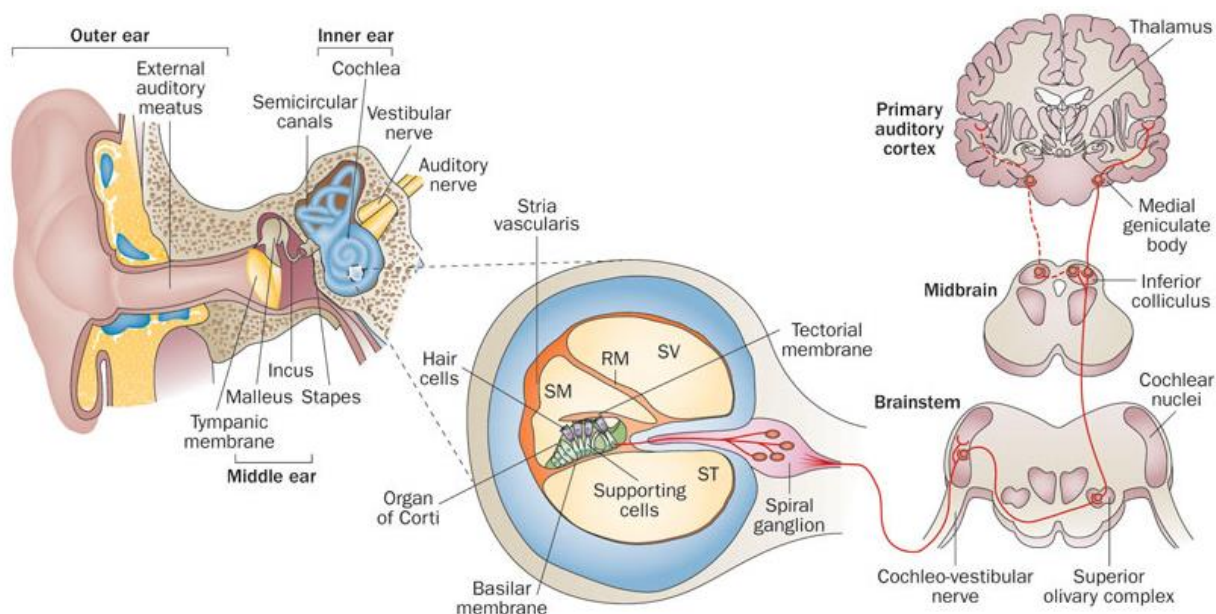


Figure 1: Human auditory system (Ng. L et al., 2013)

Solvents and Asphyxiants are found to disrupt intrinsic anti-oxidant defences and make the ear more vulnerable to the exposure to noise (Morata, 2012). Researchers also observed that ototoxic solvents might modify the membranous structures of the outer hair cells making them fragile and vulnerable. Thus, with the same acoustic energy, co-exposure to ototoxic solvents might exacerbate hearing damage. The solvent could also reduce the protective role played by the middle ear, allowing the penetration of more acoustic energy and therefore causing further hearing damage (Campo et al., 2013; Hodgkinson et al., 2006). Solvents such as Toluene and Styrene are found to affect hearing through chemical poisoning of hair cells, resulting in disorganization of their membranous structures. 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 (Campo et al., 2013).

For chemicals, such as n-hexane, n-heptane, carbon disulphide, lead and mercury, the auditory effect is connected to the neurotoxic effect (substances which may affect the central or peripheral nervous system) of these substances. Thus, they exhibit more central neurotoxic effects than pure ototoxic effects (Morata, 2012). Exposure to heavy metal such as Lead might impair conduction in the auditory nerve and the auditory pathways in the lower brainstem (Bleecker et al., 2003). When the outer hair cell is affected by the increased blood lead, it might lose the protective damping effect for the inner hair cells causing the inner hair cells to be more easily damaged with exposure to the less attenuated sound levels (Hwang et al., 2009). Exposure to high concentrations of Trichloroethylene has been shown to disrupt cochlear sensory hair and spiral ganglion cells as well as the auditory nerve pathways within the cochlea (Campo, et al., 2013). Carbon disulphide, mercury, and some pesticides have been found to be associated with auditory effects in humans (Morata, 2012).

## 6. STRATEGIES FOR HEARING CONSERVATION

In absence of sufficient scientific data for the development of occupational exposure levels (OEL) for ototoxic agents, the following recommendations are made in the literature for prevention of hearing loss from co-exposure to noise and ototoxic agents.

- A “noise notation” has been proposed to indicate an increased risk of hearing loss after exposure to ototoxic agent at a level close to the occupational exposure level (OEL) with concurrent noise exposure. The noise notation has been adopted by Sweden, France and Switzerland (Morata, 2012).

- Material Safety Data Sheets (MSDS) generally do not indicate the ototoxicity of different solvents and pesticides. Thus, a significant challenge is developed for risk identification, risk assessment and risk management. It is therefore recommended that effort should be given to collect, combine, evaluate and collate the available scientific data for a clearer understanding for the non-experts (Nies, 2012).
- Pure-tone air-conduction audiometry (PTA) is the commonly used clinical test both in the United States and Europe to measure the extent of temporary and permanent hearing loss. However, it has been found inadequate for examining hearing loss from mixed exposure to noise and ototoxic agents. 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 (such as Distortion Product Otoacoustic Emissions (DPOAEs)) that evaluate the auditory system more comprehensively, from the cochlea to the higher auditory pathways. This test may help differentiate between the individual (and the combined) effects of noise and ototoxic agents on hearing (Campo et al., 2013).
- Another recommendation is that an assessment of the loss of communication skills, a middle-ear test (a quick measure of the stapedial reflex), and questionnaires on exposure to chemicals should be carried out to allow early detection of hearing loss due to exposure to noise and ototoxicity. This recommendation is established from the fact that sounds are perceived not only as less loud, but also as distorted and word recognition may also be compromised due to the combined exposure to noise and ototoxic agents (Campo et al., 2013).
- Occupational health professionals, employers and the workforce should be made aware of the risks associated with ototoxic substances and workers exposed to them should be included in hearing conservation programs. Ototoxicity should also be made part of occupational health-screening activities (EU-OSHA, 2009; Nies, 2012).
- Noise exposure limits should be reduced for workers exposed to both noise and ototoxic agents as a precautionary measure (Burgess & Williams, 2006).
- Occupational risk assessment and monitoring strategies must include assessment of all hazardous agents (not restricted to noise) and control of exposures; inclusion of workers exposed to ototoxic chemicals in hearing loss prevention programs; careful analysis of audiometric results and referral of cases of hearing loss that do not seem to be exclusively related to the noise exposure (Morata, 2012).
- The Australian Institute of Occupational Hygienists (AIOH) Exposure Standards Committee recommended in a position paper (AIOH, 2016) that in the absence of ototoxicity information in the MSDS, workers exposed to both noise and ototoxic agents (discussed in Section 4) or even ototoxic agents alone should be included in the annual audiometric testing program for detection of any synergistic effect.

## 7. CONCLUDING REMARKS AND FUTURE RESEARCH

It is well identified and acknowledged through scientific studies that hearing damage is often a concern in the workplace where there is an exposure to either excessive noise or ototoxic agents on their own. The literature review in this paper has presented very clearly the synergistic effect of combined exposure to noise and ototoxic agents on workers' hearing. The authors stress that a comprehensive and methodological scientific approach is required to battle this occupational hazard. Occupational noise assessments must document the presence of any ototoxic agent, its exposure level in the workplace and establish the characteristics and exposure level of noise at different work areas/activities. While ranking the noise hazard area/source for establishment of a priority list, the presence of ototoxic agents should be listed alongside and areas with combined noise and ototoxic exposure should be given priority, for further investigation and implement of management and control measures. Material Safety Data Sheets should be updated with information on ototoxicity such that the "hearing risk" is known to the end user and the information can be readily available during noise assessment in the respective work areas. In this connection, a "noise notation" concept may be used which is already adopted in Sweden, France and Switzerland to indicate the increased risk of hearing at combined exposure. In addition to pure-tone audiometric tests, Distortion Product Otoacoustic Emissions (DPOAEs) or similar should also be considered to differentiate between the individual (and the combined)



effects of noise and ototoxic agents on hearing. Furthermore, an assessment on the quality of communication and speech/word recognition of the workers might be useful for early detection of hearing damage with combined exposure. Reducing the permissible exposure level of both noise and ototoxic agents would limit the hearing damage on either dimension of the exposure (noise or ototoxic exposure) and hence engineering and administrative control measures would be much more effective in taking care of the extent of hearing damage at combined exposure.

For future research, a comprehensive database needs to be developed across industries to include the different types of workers exposed to both ototoxic agents and noise either in isolation or in a combination with relevant exposure information, personal details such as age, sex, noise sensitivity, prevailing medical condition and audiometric test investigation details etc. Artificial Intelligence (AI) and Artificial Neural Network (ANN) can then be employed to predict the hearing loss and establish the exposure-response relationship. These are emerging as promising techniques in such applications in recent years (Rehman et al., 2012, Aliabadi et al., 2015).

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