Chapter

Occupational Hearing Loss

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Abstract

Occupational hearing loss received attention after the Industrial Revolution and through World Wars I and II. It currently accounts for the largest portion of occupational diseases, and a third of all hearing loss is due to noise. Occupational hearing losses include noise-induced hearing loss (NIHL), hearing loss caused by ototoxic substances and hearing loss caused by their complex interactions. In the case of NIHL, even when exposed to the same noise, the degree of hearing damage and recovery may vary from person to person, and also be affected by other noise in daily life. Various organic solvents and some heavy metals exposed in workplace are important causes of ototoxic hearing loss, and they are known to have additive or synergistic effects when accompanied by noise. In Korea, NIHL is the most common occupational disease and has been increasing continuously since the 1990s. The number of claims for compensation has also been increasing steadily. However, the developed country including Korea almost never considered the effects of chemicals on the diagnosis and compensation for hearing loss workers. Occupational hearing loss can be prevented through hearing conservation programs. In this chapter, we will introduce the scientific basis of noise induced hearing loss, the impacts of ototoxic substance and co-existence impact on hearing loss.

Keywords: occupational hearing loss, noised-induced hearing loss, noise, solvents, ototoxicity, co-exposure

1. Introduction

1.1 Noise-induced hearing loss

Occupational noise exposure is very common around the world. Up to 25% of workers are exposed to workplace noise above 85 dB(A) (weighted decibel relative to human ear) [1]. Noise-induced hearing loss (NIHL) is the second most common cause of hearing loss after age-related hearing loss (ARHL) and 16% of adult hearing loss is estimated to be caused by workplace noise [2]. In addition, one-third of workers exposed to noise showed audiometric evidence of NIHL, with 16% experiencing material hearing loss [3, 4].

The prevalence of NIHL is increasing worldwide. Prevalence in Korea is also increasing, especially over the past 20 years. Cases of accepted compensation for NIHL are more rapidly rising from 2016 than the cases for audiometric diagnosis (**Figure 1**).

Hearing loss is associated with cognitive decline and depression, and now accepted as a risk factor for dementia [5]. Noise from by daily life (subways, electric tools) or hobby (music concerts, sports viewing, hunting, etc.) can also contribute to hearing loss.

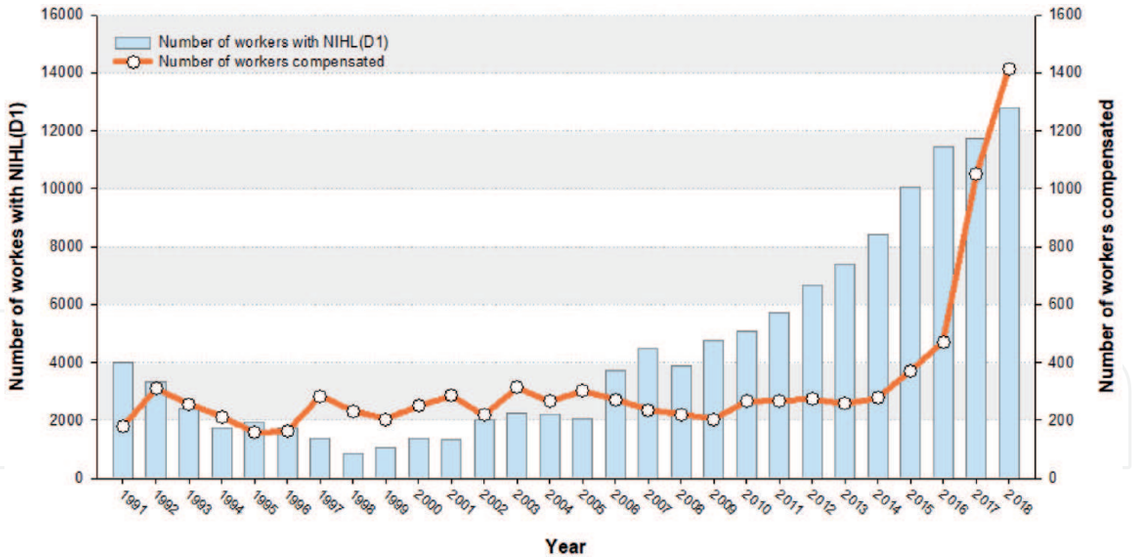

Figure 1.
Prevalence of noise-induced hearing loss (D1) and compensated cases in Korea by year (1991 to 2018). Prevalence of noise-induced hearing loss (D1) (in blue bars) and cases for compensation (in red line) have increased from 1991 to 2018. Diagnostic criteria of NIHL in Korea requires hearing loss more than 30 dB on average threshold across 0.5 kHz, 1 kHz, and 2 kHz and more than 50 dB at 4 kHz. If the average threshold exceeds 40 dB, decision for compensation could be made. The compensated cases for NIHL were increasing more sharply since 2016, whereas the diagnosed cases were increasing more steadily. http://www.kosha.or.kr/kosha/data/healthExamination.do. http://www.moel.go.kr/policy/policydata/view.do?bbs_seq=20200401401.

There are jobs where hearing is very important due to the nature of work itself or safety concerns. Hearing loss reduces speech recognition ability in the noisy environment and hearing protection devices (HPDs) also hampers speech recognition in noise. When hearing impaired workers wear a HDPs, their difficulty increases in hearing warning signals. There was association between the severity of hearing loss and the risk of work-related injury requiring hospitalization [6]. Even in the workplace where hearing is less important, hearing loss is a major cause of stress-related sick leave [7]. Economic impact of NIHL on social burden includes lost productivity, absenteeism, reduced income and tax revenues, welfare payment and compensation, special education, vocational rehabilitation programs, and health care [8].

The purpose of this review is to have a comprehensive overview of NIHL including pathophysiology, diagnosis, prevention, and to understand the recently emerging topics on noise-induced cochlear synaptopathy.

1.2 Pathophysiology

Noise-induced hearing loss is a complex disease caused by the interaction of genetic and environmental factors. It is usually caused by chronic loud noise exposure but also could be caused by transient or repetitive acoustic trauma of very high intensity, resulting in greater damage [9]. The total energy level of noise causing NIHL is determined by the intensity of the noise and the total exposure time. The noise at the same total energy level will cause the same amount of cochlear damage [10].

The inner ear damage caused by noise is divided into temporary threshold shift (TTS) and permanent threshold shift (PTS) depending on the duration of the hearing loss. Hearing loss recovers within 24–48 hours in TTS, while it is irreversible in PTS. Mechanisms of TTS and PTS are considered to be different. Animal study showed that TTS in early life can accelerates age-related hearing loss (ARHL) [11]. However, long-term impact of TTS in human ear is lacking. Pathology of

noise induced damage is the loss of outer hair cells leading to threshold elevations and poorer frequency discrimination. Main threshold shift occurs at an half octave higher than the frequency of loud noise, with the largest damage at 4 kHz and the smallest at 0.5 kHz [12]. Susceptibility around 4 kHz is associated with the mechanical properties of the middle ear and resonance frequency of external auditory canal [13].

Mechanism of cochlear pathology can be categorized into mechanical and metabolic [12]. Metabolic damage is a major mechanism of NIHL from chronic exposure to noise. Characteristic finding is loss of hair cells as a result of increased free radicals such as reactive oxygen species (ROS) and reactive nitrogen species within cochlear hair cells [14]. Damage starts in outer hair cells in row 2 and 3 of most vulnerable area to noise, possibly as a result of necrosis [15]. Noise releases ROS from mitochondria into cytoplasm of hair cells via release of Ca^{2+}. Cytoplasmic ROS leads to production of pro-inflammatory cytokines and pro-apoptotic factors, finally to apoptosis of hair cells. Free radicals can persist for 7–10 days after cessation of noise exposure, which could induce progressive cochlear damage [16]. Noise-induced ischemia and reperfusion also increase the generation of ROS [14]. Lipid peroxidation induced by ROS acts as a toxic substance, causing apoptosis [15].

When the noise is extremely loud over 130 dB SPL, mechanical damage could occur via excessive vibrations of the delicate cochlear structures. Breaking or fusion of stererocilia of hair cells are most specific morphopathology. Noise could damage other cochlear structures; damage to cochlear vasculature, loss of fibrocytes, rupture of attachments of stereocilia tips to the tectorial membrane, distension or rupture of tip links, damage to pillar cells, and rupture of dendrites [14]. Noise could crumple pillar cell, decreasing length of the OHC, and detaching stereocilia from tectorial membrane in reversible way, which is understood as a mechanism of TTS [17].

Recent hot topic on noise-induced damage on auditory system is cochlear synaptopathy. Until recently, noise that does not cause threshold shift was considered safe. However, recent animal experiments have shown that noise exposure that does not cause hair cell loss may damage ribbon synapse between inner hair cell and spiral ganglion neuron [11]. Cochlear inner hair cells (IHCs) are important as mechano-electrical transducer of auditory information. Receptor potential generated by IHCs releases the neurotransmitter at the synaptic end, while outer hair cells work as cochlear amplifier via process of electromotility which increases the vibration of basilar membrane. Synaptic ribbon is specialized electron-dense structure, which is anchored to pre-synaptic membrane only nanometers apart. It contains large pool of "readily releasable" vesicles to finely vary synaptic output continuously in sensory organ of hearing and vision [18]. Thus, damage of ribbon synapse between IHCs and spiral neurons results in improper conveyance of neural information to auditory nerve fiber. Noise causes damage of presynaptic ribbons and postsynaptic nerve terminals showing various degree of swelling. The mechanism of damage for postsynaptic terminal is glutamate-mediated excitotoxicity, while mechanism of ribbon loss is unclear [19]. In cochlear synaptopathy, hearing threshold is normal because OHC is undamaged, but the amplitude of auditory nerve activity decreases as a result of silenced auditory nerve fibers [20].

Auditory nerve fibers (ANFs) could be functionally categorized by their spontaneous rate (SR). High-SR ANFs respond to sound at threshold level, whereas low-SR ANFs react to loud sound, follow rapid amplitude changes of acoustic signal, and are considered to have an important role in the hearing in noisy environment due to their larger dynamic range. Low-SR ANF appears to be damaged selectively after noise exposure [20]. Because it causes functional hearing loss without threshold change, it is also called "noise-induced hidden hearing loss".

Cochlear synaptopathy could be permanent and lead to a degenerative death of the spiral ganglion neuron [21]. The results of human studies on cochlear synaptopathy are controversial. If the cochlear synaptopathy is confirmed in human subjects, the conventional belief that noise would be safe if it does not cause a threshold shift should be changed [19].

1.3 Individual susceptibility

Severity of cochlear damage after noise exposure varies among individuals. Genetic factors would account for the different susceptibility up to 50% [22]. In animal study, genetic deficits leading to ARHL predispose the inner ear to NIHL [23]. Single Nucleotide Polymorphism (SNP) is the most common site of genomic mutations. It is estimated that the SNP of K^+ recycling gene and heat shock protein (HSP) gene in the inner ear is associated with the sensitivity of NIHL [24, 25].

ISO 1999:2013 model assesses the risk of NIHL with age, gender in addition to intensity of exposed noise and exposure time in years [26]. The prevalence of NIHL is higher in male than in female and racial difference exists with lower prevalence in darker pigmentation [27]. Increasing age, smoking, poor diet, lack of exercise, comorbidity such as diabetes, cardiovascular disease may increase risk of NIHL [28]. Sufficient nutrition helps to preserve high frequency hearing [29].

1.4 Noise exposure levels by occupational group

The prevalence of hearing loss among noise-exposed workers is various across industries and occupations. Noise exposure is common in industries of mining, construction, manufacturing, forestry, utilities, repair and maintenance, and transportation sectors [2]. Sixty-one percent of the mining workers, 51% of the construction workers, and 47% of the manufacturing workers are exposed to noise [1]. Among workers of the above industry sectors, 20 ~ 25% have a material hearing impairment [30]. In Korea, NIHL was most common in the workers of manufacturing sector, followed by construction sector (**Figure 2**).

1.5 Diagnosis

Audiometric evidence of NIHL is characteristic notch or bulge between 3 kHz and 6 kHz, mostly worst at 4 kHz, with preserved hearing at 8 kHz and lower frequencies [31]. Notch deepens and widens with continued noise exposure, eventually involving lower frequencies. Hearing aggravates in the first 10–15 years of noise exposure, and then process slows down [17]. The maximum hearing loss from NIHL has been accepted not to exceed 75 dB at higher frequencies and 40 dB at lower frequencies [32]. However, it could reach 80 dB or worse in 2.6% of construction industry engineers [33]. Notch could be observed in 19.9% of persons without history of loud noise exposure, so audiometric notch does not necessarily mean NIHL [3].

Unlike NIHL, the ARHL accelerates over time. Hearing loss in ARHL starts at 8 kHz or higher frequencies and expands to lower frequencies. When NIHL and ARHL coexist, the notch widens and looks like a bulge [34]. As the combined ARHL progresses with advanced age, noise notch may be rarely observed [35]. Sometimes medicolegal opinion is sought about which factor contributes more on the etiology of hearing loss between noise and age. It is impossible to distinguish the allocation of each factor in aged persons.

Hearing in noise may be compromised probably due to cochlear synaptopathy. To quantify damage from noise exposure, speech recognition in quiet and noise is

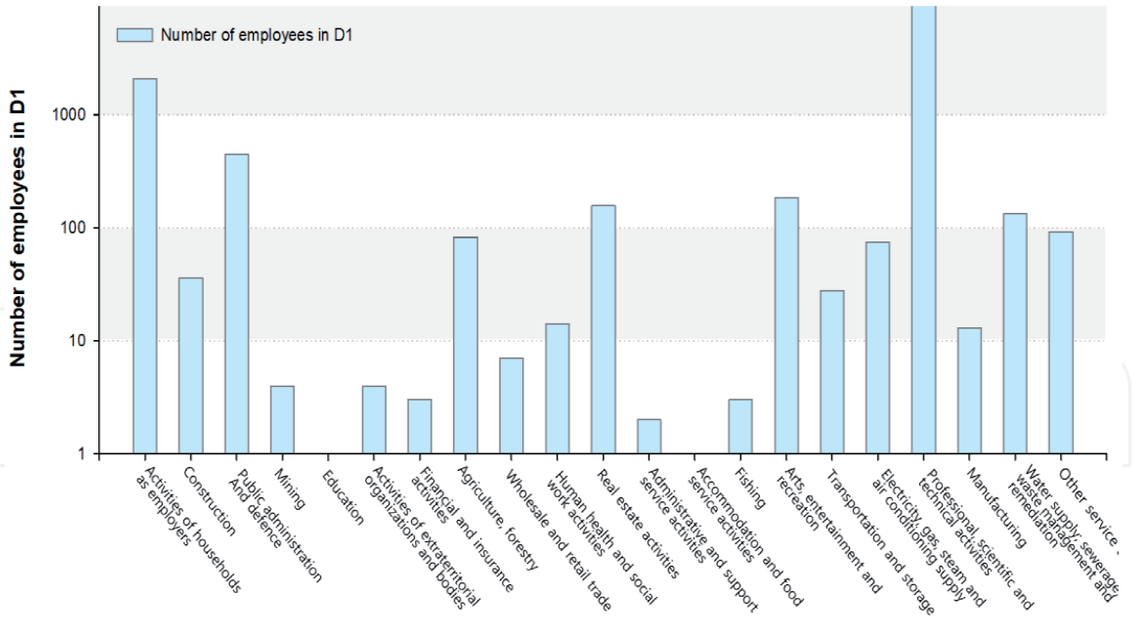

Figure 2.
Prevalence of noise-induced hearing loss (D1) according to Korean standard industrial classification. A total of 12,822 cases were diagnosed as NIHL in 2018 in Korea. Among them, NIHL was most commonly reported in manufacturing sector with 9,455 cases, followed by construction, mining, transportation, and business facility management and business support services sectors. http://www.kosha.or.kr/kosha/data/healthExamination.do.

also recommended [21]. Otoacoustic emission (OAE) can be used as an earlier test before PTA deficit is evident [36]. But recent studies showed that OAE was not more sensitive than PTA in assessing hearing loss caused by long-term exposure to noise [37]. Possibility of middle ear acoustic reflex as a diagnosis of cochlear synaptopathy was also suggested [38].

1.6 Asymmetric NIHL

Noise-induced hearing loss is typically bilateral because noise affects both ears symmetrically. However, it could be asymmetric. Prevalence of asymmetric hearing gap larger than 15 dB in general population is 1% while those of NIHL were reported as 4.7–36% [35]. Left ear was more affected, especially in male [39, 40]. Lateral difference was most prominent in 3–6 kHz [41]. The firefighters and public safety workers may no longer be able to carry their duties because asymmetric hearing disturbs to distinguish sound direction and causes work-related risk [42].

There are two theories about mechanism of lateral asymmetry. One is head shadowing effect that makes noise level affecting each ear unequal [43]. Another is that left ear is more susceptible to noise damage for physiological reasons. It involves a less sensitive acoustic reflex in left side and a stronger protective auditory efferent system of the right olivocochlear bundle [44, 45].

MRI scan should be performed to rule out vestibular schwannoma in asymmetric hearing loss. Medicolegal decision of asymmetric NIHL is quite unconvincing. According to Robinson's criteria, if there is no evidence of NIHL in the better ear, patients can be declined compensation [45]. Whereas, Fernandes et al. insisted that comment should be made on the causation as being noise-induced, if there is no other cause to explain the asymmetry [46].

1.7 Tinnitus and hyperacusis

The prevalence of tinnitus among noise-exposed workers is 24%, which is much higher than that of the general population [47]. Tinnitus is bilateral in majority of

workers exposed to noise, however, some of them complains of unilateral symptom, more commonly in left ear [48]. Tinnitus degrades quality of life in workers and distracts military personnel during military operation [49]. Although association of noise and hyperacusis have rarely been studied, pop and rock musicians were at high risk for the development of hyperacusis [50].

1.8 Noise and dizziness

Besides hearing loss, noise can induce vestibular dysfunction through the damage to sacculocolic reflex pathway or damage to vestibular hair cell [51, 52]. The relationship between NIHL and abnormal vestibular evoked myogenic potentials (VEMPs) was reported in human study [53]. Noise exposure reduced the stereocilia bundle density of the vestibular end organ and reduces the firing rate of the anterior semicircular canal (ASCC) without significant change of the vestibular-ocular reflex, suggesting possibility of "hidden vestibular loss" [52]. Abnormal electronystagmography (ENoG) was more common in the asymmetrical NIHL group than in symmetrical NIHL [54].

1.9 Prevention

Noise regulation is the best option to prevent NIHL. Current noise regulations are based on the intensity of chronic continuous noise rather than impulsive acoustic trauma. Degree of exposure is calculated as registered in individual reporting or hearing protection programs [30]. Noise of intensity below 80 dB (A) (weighted decibel relative to human ear) reduces the risk of NIHL [55]. Daily permissible exposure limit (PEL) and exchange rate should be set to run hearing conservation program. Many countries legislate PEL at 85 dB(A) for an 8-hour workday. Some countries loosely permit up to 90 dB(A). Exchange rate defines the 3–5 dB increase in noise intensity with which exposure time should be halved to protect hearing. Exchange rate of 5 dB appears to be more accurate than 3 dB [56]. For example, 4 hours of exposure to 90 dB(A) is as hazardous as 8 hours of exposure to 85 dB(A). Number of workplaces of which noise exceeds PEL of 85 dB(A) for an 8-hour workday has been decreasing in Korea. It reduced from 20.2% of total workplaces in 2014 to 15.3% in 2018 (**Figure 3**). For impulse noise, 140 dB is generally set as the upper limit [57].

Hearing protection devices (HPDs), including earmuffs and earplug, are secondary level personal protection. Most workplace noise can be attenuated to a safe level by reducing noise by 5–10 dB, and this goal can be achieved when if HPDs are worn properly and continuously [30]. However, many workers do not wear HPDs for enough time and the effect is cut in half if workers remove HPDs for only 30 minutes of an 8-hour workday [58]. Therefore, it is efficient, when selecting HPDs, to focus on consistency of use than noise reduction rate of HPDs [59]. Individual fit-test system for earplugs is more feasible for field use and could effectively prevent hearing deterioration [60]. Earmuffs can reduce noise more consistently than earplug, and 3D print earmuffs made from light materials such as acrylonitrile butadiene styrene/clay nanocomposites was helpful in reducing weight of earmuffs and would probably increase comfort [61]. Hearing conservation program in elementary school are potentially effective way to know the risks of noise exposure early in life, leading to behavioral changes such as noise reduction and HPDs [62].

It is important to reduce the "know-do" gap between knowledge accumulated to prevent NIHL and actual implementation at workplace. This requires frequent

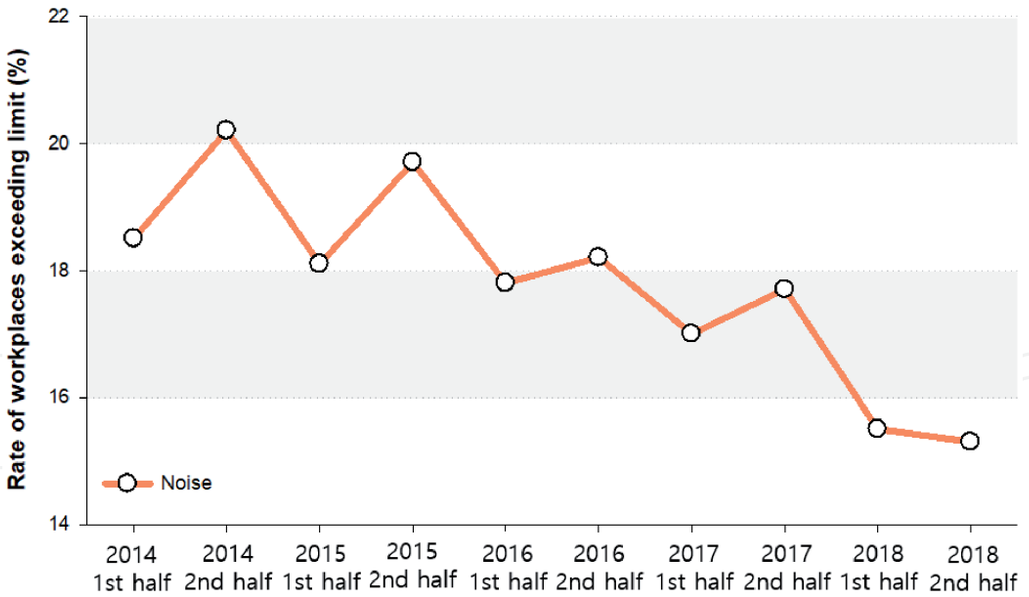

Figure 3.
Korean workplaces of which noise exceeded permissible exposure limit (2014 to 2018). Percentage of Korean workplaces of which noise exceeded permissible exposure limit was 21% until 2010 but is gradually decreasing. In the second half of 2018, it was 15.3% showing the lowest rate for the past 5 years. https://www.moel.go.kr/info/publict/publictDataView.do;jsessionid=adRh47EovBcKL142q0R3sKQStfieMxcEVFYSD2NXqjie0s2D438avLaPebxaainR.moel_was_outside_servlet_www1?bbs_seq=20200200123.

communication meetings for noise control, assigning staff to provide daily program support, noise hazard identification, selection of HPDs, and providing inexpensive sound level meters or sound measuring apps [30].

We suggest that hearing conservation program should include administrative or engineering controls to reduce sound levels. Workplace noise should be monitored using either a wearable sound level meter or a dosimeter to determine if noise exposure level is at or above 85 dB(A). If the workplace noise exceeds an 85 dB(A) for an 8-hour workday, exposed employees should be enrolled in a hearing conservation program (HCP) and audiometric test should be conducted annually by audiologist to check if the standard threshold shift occurs. Employees enrolled in HCP should be offered HPDs and take mandatory training program annually about effects of noise on hearing, purpose and value of HPDs and hearing test. Managers or supervisors must attend training sessions and should keep the record of all hearing tests, noise surveys, and training records.

1.10 Pharmacotherapy

There is no practical medication to prevent NIHL from chronic noise exposure. Most drugs have been studied either on an experimental level or on an animal study basis.

The noise exposure increases the immune and inflammatory factors in the cochlea. Steroids are the only approved medicine in treating sudden hearing loss. Animal study showed that steroids before and after the exposure to acoustic trauma were effective through control of the inflammatory response [63, 64]. It is estimated that intratympanic steroid injection would be effective in protecting outer hair cell efferent terminal synapse, and intraperitoneal steroid injection would be effective in protecting organ of Corti and stria vascularis [65]. In human studies, combined systemic & intratympanic steroid administration was more effective than systemic steroid only [66]. Long-term administration of steroid is inadequate due to its possible side effects.

Free oxygen radicals and oxidant stress are important pathological mechanisms of NIHL. N-acetylcysteine (NAC) is an antioxidant and is known to reduce noise-induced ototoxicity in animal study. There was no significant differences of overall hearing loss in military population between NAC group and placebo group [67].

Neurotropin-3 (NT3) and Brain derived neurotrophic factor (BDNF) are known to be important factors in the generation and maintenance of cochlear hair cell ribbon synapse [68, 69]. Animal study demonstrated a reduction in synaptopathy and a restoration of hearing immediately after strong noise exposure [70] but human data is lacking.

1.11 Conclusion

Noise-induced hearing loss is drawing more attention than ever before. Besides hearing loss, noise can also compromise the vestibular function. Recently, evidence on noise-induced cochlear synaptopathy is accumulating. Exposure to noise in short duration or less intense noise may result in functional hearing loss without threshold change on audiogram. So far, prevention is the best option, but we expect that continuous research on NIHL will open up the possibility for treating drug ototoxicity and ARHL as well.

2. Chemical induced hearing loss

2.1 Introduction

Chemicals such as organic solvents, metals and asphyxiants are known for their neurotoxic effects on both the central and peripheral nervous systems. These agents could injure the sensory cells and peripheral nerve endings of the cochlea [71].

Over the past 3 decades, several studies investigated the relationship between occupational exposure to chemical substances and hearing loss for humans [72]. According to the score combining human and animal data, lead (and its inorganic salts) as an only inorganic substance and the organic chemicals including toluene, styrene, and trichloroethylene were ranked as “ototoxic”. Other candidate substances classified as “possibly ototoxic” are nitriles (acrylonitrile, 3-butenenitrile), carbohydrates (n-hexane, p-xylene, and ethylbenzene), hydrogen cyanide, carbon monoxide, carbon disulfide, and mercury, germanium, and tin. Recently, a classification criteria on ototoxic substances was delivered by the Nordic Expert Group (NEG). The NEG chose a quantitative approach, meticulously comparing the “no observed” or “lowest observed” effect levels with occupational exposure limits from various countries. This information can be useful for the management of toxic substances and prevention of hearing loss (**Table 1**) [73].

Until now, regarding regulatory problem, the interaction with noise has not been investigated in a satisfactory way. Although it is very difficult to combine all of the data to arrive at solid conclusions, this does not exclude the possibility of other chemical substances can worsen hearing losses due to noise.

2.2 Organic solvents induced hearing loss

In workplace, one of the most common kinds of exposure is solvents mixture. The most prevalent exposures seem to happen in industries where workers have contacts with paints, thinners, lacquers and printing inks [74]. In Korea, organic solvents have the second highest excess rate among harmful factors in workplaces.

Classification	Criteria	Ototoxic substances
Category 1	Human data indicate auditory effects below or near the existing OELs. There are also robust animal data supporting an effect on hearing resulting from exposure	toluene, styrene, carbon monoxide, carbon disulfide, lead and mercury
Category 2	Human data are lacking, whereas animal data indicate an auditory effect below or near the existing OELs.	p-xylene, ethylbenzene, and hydrogen cyanide
Category 3	Human data are poor or lacking. Animal data indicate an auditory effect well above the existing OELs.	Other substance

OEL: occupational exposure limits.

Table 1.
Classification and the criteria of ototoxic substances based on occupational exposure limits.

The exceeded rate of the occupational exposure limit maintained a similar level of 0.4 to 0.7% for the last five years from 2014 to 2018 (**Figure 4**). Although the ototoxic effects of organic solvents have been widely studied, there is no consensus about the correlation between the solvents exposure level and the resultant hearing loss.

In occupational condition, the ototoxicity of organic solvents is more difficult to prove. Because the workplace concentration of chemicals is much lower than that used in animal studies, and the workers are usually exposed to a mixture of solvents with widely varying compositions and concentrations, it is difficult to assess the effect of a single substance. Furthermore, in industrial settings, exposure to chemicals often coexists with an elevated level of noise, which makes it difficult to distinguish the solvent effect from the noise-induced hearing loss [22].

Recently, Hormozi et al. reported dose–response relationship between organic solvents mixture exposure and risk of hearing loss from a meta-analysis [72]. The results showed a statistically significant dose–response relationship between the occupational exposure level (Exposure Index, EI), duration of exposure or number of solvents and the risk of developing hearing loss (**Table 2**).

2.3 Mechanism of organic solvent ototoxicity

Long-term exposure to organic solvents has been shown to cause irreversible hearing impairment damaging the cochlear hair cells as the first target [75]. The mechanism of acute injury would be the direct action of solvents on the cells of the organ of Corti, resulting in disorganization of their membranous structures, whereas chronic ototoxic effects may be explained by the formation of chemically and biologically reactive intermediates [76].

The ototoxicity mechanisms with strong evidence were described in **Table 3**. These solvents adversely affect both peripheral and central auditory system. For example, toluene may enhance inhibitory synaptic responses as CNS depressants, also can inhibit the middle-ear acoustic reflex (cholinergic efferent system). This would make inner ear more susceptible to co-exposure even to a noise intensity below permissible limit value [77].

Śliwinska-Kowalska (2007) summarized a risk/odds ratio of organic solvent-induced hearing loss, compared to non-exposed population, as followings. 1) No excess risk was found for workers exposed to solvent mixture when: the exposure history was short (up to 4 years), or the exposure level was very low (current exposure ranged from few to 18 ppm for toluene, to few ppm for xylene and other

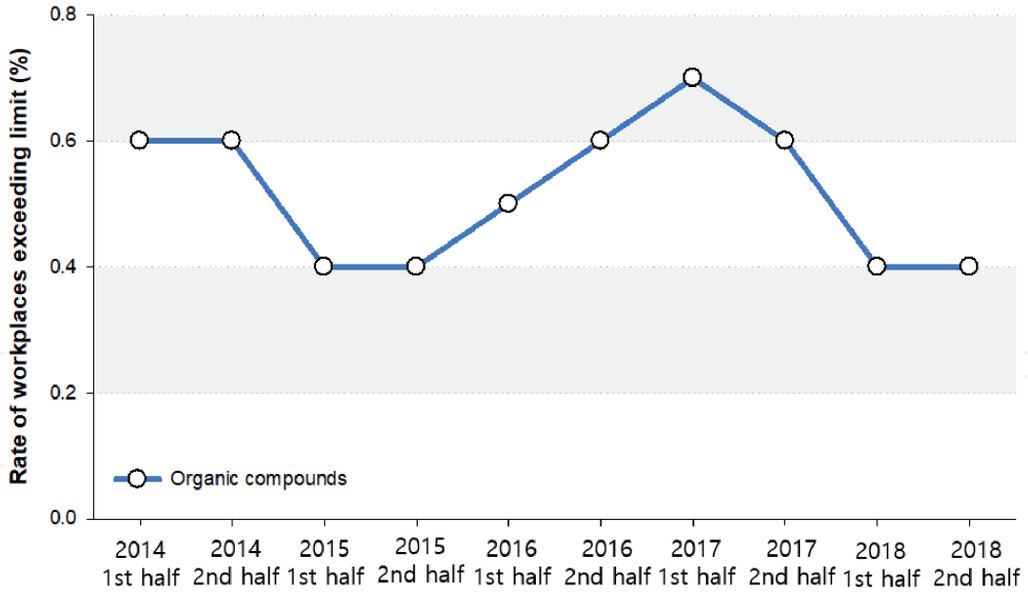

Figure 4.
Korean workplaces of which organic solvents exceeded permissible exposure limit (2014 to 2018). https://www.moel.go.kr/info/publict/publictDataView.do;jsessionid=adRh47EovBcKL142q0R3sKQStfieMxcEVFYSD2NXqjieos2D438avLaPebxaainR.moel_was_outside_servlet_www1?bbs_seq=20200200123.

Variable	Reports (n)	OR (95% CI)†	p
Duration of exposure			0.001
< 5 years	4	1.01 (0.92–1.10)	
5–10 years	3	1.57 (1.27–1.93)	
> 10 years	7	3.36 (2.36–4.79)	
Exposure index (EI)‡			0.049
< 0.5	3	1.37 (0.75–2.48)	
0.5–0.99	3	3.25 (1.88–5.62)	
≥ 1	7	4.51 (3.46–5.90)	
Solvents			0.045
2–5	7	1.62 (1.07–2.44)	
6–8	4	4.22 (2.72–6.56)	

**Hearing loss: average hearing threshold greater than 25 dB in at least one ear (250–8000 Hz).*
†Reference group: not exposed to either noise or solvents mixture.
‡EI: the sum of the mean time-weighted exposures to each solvent was divided by its occupational exposure limit (American Conference of Governmental Industrial Hygienists threshold limit value, ACGIH TLV).
Cited from THE RISK OF HEARING LOSS ASSOCIATED WITH OCCUPATIONAL EXPOSURE TO ORGANIC SOLVENTS MIXTURE WITH AND WITHOUT CONCURRENT NOISE EXPOSURE: A SYSTEMATIC REVIEW AND META-ANALYSIS. International Journal of Occupational Medicine and Environmental Health 2017;30(4):521–535 https://doi.org/10.13075/ijomeh.1896.01024.

Table 2.
Dose–response relationship between organic solvents mixture exposure and risk of hearing loss.*

solvents, and the exposure index was <1). 2) Excess risk was found for workers exposed to solvent mixture when: the exposure level was moderate (toluene exposure ranged from 25 to 70 ppm, xylene exposure 25–40 ppm, and exposure index from 0.3–1.53), or the workers were exposed to high solvent concentrations and noise (the mean lifetime exposure to xylene was 696 ppm, to toluene 203 ppm, and the mean exposure index was 6.3) [72]. Risk/odds ratios of hearing loss due

Chemicals	Targets and impacts	Mechanism	Points to consider
Aromatic solvents	Target: Central nervous system, cochlear hair cell Impact: Enhancement in inhibitory synaptic responses, affecting middle-ear acoustic reflex.	1. In case of acute effect, direct action on the cells of the organ of Corti. 2. In case of chronic effect, formation of intermediates such as reactive oxygen species. 3. Cause K^+ flow dysfunction. 4. Outer hair cell toxicity due to K^+ massive efflux and tunnel accumulation.	1. Prolonged exposure causes irreversible hearing impairment. 2. Affect the middle-ear acoustic reflex, which partially explain the synergistic effects of co-exposure to noise and aromatic solvents.
Nitriles	Target: cochlear hair cell, spiral ganglion cells Impact: Reduces high-frequency hearing sensitivity and enhances noise-induced hearing impairment.	1. Induce loss of inner ear hair cells and spiral ganglion cells. 2. In the case of acrylonitrile, the risk of oxidative damage to the inner ear is increased due to damage to the cellular antioxidant defense mechanisms.	Permanent hearing damage may occur due to combined exposure with noise.
Halogenated hydrocarbons	Target: Outer hair cell	In the case of polychlorinated biphenyls (PCB), it is assumed to have a direct effect on outer hair cells.	Presumed to be a sequelae of thyroid disease caused by halogenated hydrocarbons.
Trichloroethylene	Target: Cochlear sensory hair cell, spiral ganglion cells, auditory nerve pathways	Unknown, but dose dependent hearing loss	Hearing loss tends to occur only at high level of exposure.

Table 3.
Summary for impacts and mechanisms of ototoxic chemicals in workplace exposure.

to exposure to organic solvent mixture were ranged 1.4 to 5.0, while the ratio of populations co-exposed to noise and solvents were 1.7 to 8.25 [78].

2.4 Interactive effects of organic solvents and noise

Previous experiments on ototraumatic substances in animals have confirmed the synergistic adverse effects of combined exposure to noise and solvents on hearing [79, 80]. In the case of combined exposure to noise and organic solvents, depending on the parameters and characteristics associated to the noise (such as intensity and impulsiveness) and solvent (such as concentration), they might interactively affect each other.

From the animal studies, the increase in auditory brainstem response (ABR) latencies after exposure by inhalation of more than two solvents observed an additive effect rather than a synergistic or antagonistic interaction. Results of these studies imply that the mechanism of ototoxicity for these solvents may be similar.

However, rats simultaneously exposed to both toluene and noise induced a more severe hearing loss than the summated hearing loss obtained from an equivalent exposure level to each agent alone [77].

From the human studies, exposure to a mixture of solvents may damage the inner ear to a much greater extent than noise exposure. The relative risk for hearing loss in workers exposed to solvents was greater (RR = 9.6) in comparison to workers exposed only to noise (RR = 4.2). Hearing loss associated with styrene significantly increased in high frequency (8–16 kHz) and mid-audiometric frequency of 2 kHz [22]. Sliwinska-Kowalska et al. (2003) found a positive linear relationship between average working life exposure to styrene concentrations and hearing thresholds at 6 and 8 kHz. The possible synergism of combined exposure to solvents and noise on hearing has not been consistently identified in human studies. Some researchers have failed to find a synergistic effect between these agents on hearing [22].

Although it is difficult to derive a dose–response relationship between the solvent concentration and the hearing outcome, the risk of hearing loss increase with the longer duration of employment and accompanying noise in workers exposed to organic solvent [72].

2.5 Diagnostic tool for ototoxic substances

Although there is no consensus on the lowest OELs for solvents in relation to their effect on the auditory organ, the current standards for solvent-exposed populations seem to be inadequate. Since organic solvents have detrimental effects both on the peripheral and central parts of the auditory pathway, pure-tone audiogram might be insufficient to monitor their ototoxicity [78].

From previous studies, researchers have found some useful tests for the evidence of adverse effects on the central auditory system in workers exposed to mixture of solvents: 1) dichotic listening: useful tool in the assessment of solvent-exposed workers, particularly in those who have had intermediate levels of exposure; 2) electrophysiological techniques (ABR): increase of the absolute latencies and inter-peak latencies (IPL) between waves of the ABR (I-III IPL; I-V IPL; III-V IPL) or prolonged P300 (a long latency auditory evoked potential); 3) otoacoustic emissions (OAEs): gradual deterioration of hearing threshold before audiometric change; 4) comprehensive battery of behavioral central auditory function assessment procedures: solvent-exposed participants presented with poorer results adjusted for age and hearing thresholds in comparison to non-exposed subjects [77]. These tests can be conjugated to evaluate possible adverse effects of solvents on the auditory system.

2.6 Recommendations

So far, the robust evidence confirms that the effects of ototoxic substances on auditory function can be aggravated by noise, which is supported by data from epidemiologic studies on human workers.

In real world, the exposure to solvent mixtures is various in terms of levels and composition. Numerous study groups reported an association between low to moderate exposure to solvent mixtures and hearing disorders. However, occupational legislation does not take environmental chemicals hazardous to hearing into consideration. Thus, there may be numerous workers with unmet needs concerning hearing conservation.

Here we are going to make some necessary suggestions for occupational health professionals and the workforce. Health care provider should be aware of the risks related to ototoxic substances. Employers and workers should be advised

accordingly. Risk management measures aimed at reducing exposure to noise and ototoxic substances, especially co-existence of them, should be encouraged. In occupational health-screening activities, ototoxicity should be included. Appropriate diagnostic tools should be developed for early detections of chemically induced hearing impairment. Suitable scientific investigations into ototoxic properties of substance and combined effects with noise should be encouraged by well-designed studies.

Occupational noise exposure has been well-known as the most deleterious factor to hearing loss, however, the impact of chemical-induced hearing loss on workers should not be underestimated [81]. Industry-based initiatives should include the identification of populations at risk and the delivery of tailored hearing conservation program accordingly to noise and chemical-exposed workers regarding their exposure levels.

Conflict of interest

The authors declare no conflict of interest.

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