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Review of the Literature on the Links between Occupational Hearing Loss and Presbycusis

Tony Leroux
Alexis Pinsonnault-Skvarenina

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Review of the Literature on the Links between Occupational Hearing Loss and Presbycusis

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PEER REVIEW
In compliance with IRSST policy, the research results
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SUMMARY

At the request of the Executive Office of the Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST), a literature review was conducted to respond to a series of questions concerning the process that results in occupational hearing loss. The general objective of the project was to document how occupational hearing loss occurs, especially in relationship with presbycusis.

This review of the literature specifically aimed to (1) determine whether noise exposure can accelerate the progression of presbycusis; (2) establish whether using correction factors could make it possible to differentiate between occupational hearing loss and presbycusis; (3) evaluate how hearing loss progresses after the cessation of excessive noise exposure at work.

Some 30 studies published since 2000 and based on human or animal models were analyzed. The animal studies clearly demonstrated that exposure to noise accelerates the progression of presbycusis. The human studies reveal similar results. Several authors also submit that the classic concept that associates presbycusis solely with aging should be modified, and instead suggest that the loss of hearing observed with age is the result of the cumulative and synergetic effect of hearing impairment risk factors, among which is noise exposure.

Recent data, examined in this review of the literature, raise questions about the value of correction factors based on the premise that the slow degradation of hearing thresholds is only attributable to the intrinsic factor of aging, when there is evidence that some of this damage might be due to noise exposure. In the animal model, degeneration of anatomical structures related to hearing has been observed several months, even several years, after the cessation of exposure to noise. Some studies also show that impairment continues to progress beyond the simple effect of aging. While so far there are no longitudinal studies of the same nature among humans, research in this area is rapidly moving forward.

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1. INTRODUCTION

The Executive Office of the Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST) asked professor Tony Leroux of the Université de Montréal to conduct a review of the literature in order to respond to a series of questions concerning the development of occupational hearing loss, in relation to presbycusis.

The scientific opinion requested was to respond to the following questions, submitted in the contract of professional services, dated June 28, 2016:

Questions

a) Can noise exposure accelerate the process of presbycusis?

b) Can correction factors be used to distinguish occupational hearing loss from presbycusis?

c) How does hearing loss progress after the cessation of exposure to excessive noise at work? In other words, will workers who cease to be exposed to excessive noise continue to experience a decline in hearing afterward, independently of the effect of aging?

2. METHODOLOGICAL APPROACH

2.1 Literature Search Method

A preliminary literature search was carried out by the IRSST in March 2016 with the goal of documenting (1) the physiological principles of the progression of presbycusis; (2) the physiological principles of the process of developing occupational hearing loss; (3) the links between presbycusis and occupational hearing loss.

The search was carried out by using a series of English keywords to query various databases (BIOSIS Toxicology, CCHST, Cochrane Library, Current Contents Search, EMBASE, Ergonomics Abstracts, Google Scholar, ISST, OSH Update, PASCAL, ProQuest Dissertations and Theses, PubMed and TOXLINE).

The research criteria for these databases were as follows (1) publications from 2000 to 2016; (2) studies carried out on humans or animals; (3) peer-reviewed articles in journals; (4) articles published in English or French.

The database search was conducted using the following model: ([hearing loss AND noise] OR [hearing loss due to noise]) AND (risk factors OR presbycusis). For each main term, different keywords were used. These are presented in general terms in Table 1. Depending on the database queried, the keywords used could be different. The keywords used for each database are found in Appendix 1.

Table 1 – Key words used in the literature search

Hearing loss and noise	Risk factor	Presbycusis
acoustic trauma OR acquired hearing loss OR hearing impairment OR hearing loss OR hearing loss, mixed conductive-sensorineural* OR hearing loss, noise-induced* OR hearing loss, sensorineural* OR hearing loss* noise induced hearing Loss OR noise/adverse effects* noise-induced hearing loss	age factors* OR aging/pathology* OR aging* OR chemically induced OR deafness, aminoglycoside-induced OR deafness, streptomycin-induced OR excitotoxicity OR glutamate toxicity OR glutamates/toxicity* OR noise-exposed OR otoprotection OR ototoxicity OR streptomycin ototoxicity	age-associated hearing loss OR age-related hearing loss OR aging cochlea OR cochlea* OR cochlear OR cochlear diseases* OR deafness/chemically induced* OR human temporal bones OR noise-induced cochlear neuropathy OR noise-induced cochlear OR synaptopathy OR presbyacusie OR presbycuses OR presbycusis OR presbycusis*

The preliminary search found 235 references. Four articles were also provided by the principal investigator. A second search was carried out by the IRSST in October 2016 (for the period of March to October 2016), and it identified 79 other articles. A total of 318 references were thus identified by the searches. A preliminary reading of the titles and abstracts of the articles made it possible to perform an initial triage and to keep the articles related to the research questions. A total of 241 articles were rejected and 77 articles were selected for reading. From the references of the articles read, 26 other new articles were identified.

After reading these documents, 59 were excluded because they were not sufficiently relevant to the research questions. Twelve articles were set aside because they were literature reviews. They were re-read to assist in drafting this scientific opinion, but were not compiled when the strength of evidence was analyzed, because the data reported were contained in the original articles. Two studies were rejected because of their poor methodological quality (one study contained no data on noise exposure, the other study contained a selection bias which made it impossible to compare the groups under study).

Thirty studies were therefore used for the analysis. The studies described in 17 articles were conducted on human subjects, while 14 others were carried out using animal models.[1] Figure 1 illustrates the literature search process. Appendix 2 presents detailed analyses of the 30 articles accepted.

[1] One study (Mehraei et al.,2016) used both animal and human subjects and is therefore included in the two types of study, but is counted only once in the total number of studies.

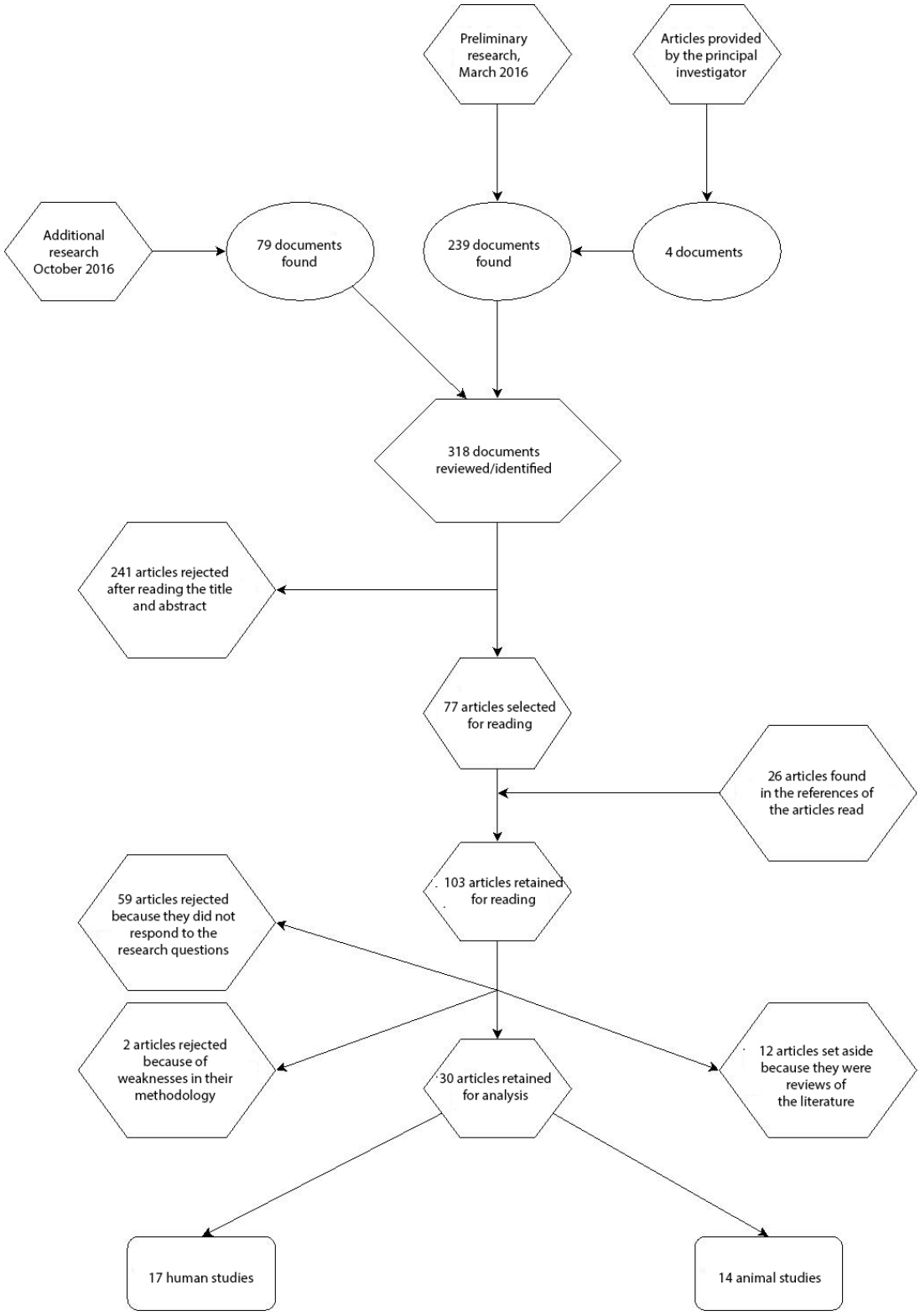


Figure 1 - Flow chart of the documentary search process.

2.2 Method Used to Analyze the Strength of the Evidence

The 30 articles retained were analyzed using the approach put forth by Ali et al. (2008). Thus, the strength of evidence of each of the articles was analyzed on the basis of seven evaluation criteria that took the form of questions. The score of each criterion varied from 0 to 2. A total score of 11 to 14 indicated an article of good quality, a score of 5 to 10 indicated an article of average quality, while a score from 0 to 4 indicated that the quality of the article was poor. The criteria used for the analysis are presented in Figure 2, while the individual analysis of the articles is presented in Appendix 3.

1. Experimental studies (levels 2 or 3)

A. Was the assignment to different groups truly randomized?
   i. If randomized control trial, random selection of participants
   ii. If experimental study, random division of participants in the groups

- If yes i or ii: 2 points
- If no i or ii: 0 point
- If the study does not include groups: 0 point

B. When the baseline measurement was taken, were the groups similar in terms of characteristics?

   i. Groups comparable to each other

- If adequate and reported (statistical tests required): 2 points
- If inadequate (e.g., are there differences between the groups at T1) and reported: 1 point
- If unreported: 0 points

C. Were the eligibility criteria specified?
   i. inclusion criteria
   ii. exclusion criteria
- If yes i and ii: 2 points
- If yes i or ii: 1 point
- If no i and ii: 0 point

D. Were the results measured in a standard, valid and reliable way?
   i. Questionnaire or test validated and reported as such in the article
   ii. The author reports the validity coefficients from the sample
- If yes i and ii: 2 points
- If yes i only: 1 point
- If no: 0 point

E. Are the analysis strategies adequately described and in line with the hypotheses?
   i. The statistical analyses are named.
   ii. The signification thresholds are named and adequate
   iii. The analyses respond to the hypothesis and are in conformity with the sample.

- If yes i to iii: 2 points
- If yes 1-2/3: 1 point
- If no: 0 point

F. Were the excluded subjects described completely?
   i. The number of excluded participants is known
   ii. The characteristics of excluded participants are known
   iii. The characteristics of the excluded participants are comparable to the study subjects.
- If yes i to iii: 2 points
- If yes to 1-2/3: 1 point
- If no i to iii: 0 point

G. Did the study adequately control for relevant demographic characteristics and confounding variables?
   i. Inclusion of relevant demographic controlled variables (e.g., age, education)
   ii. Inclusion of relevant controlled variables other than demographic
- If yes i and ii: 2 points
- If yes ½ i: 1 point
- If no i and ii: 0 point

Figure 2 - Analysis table used to evaluate the quality of articles.
(Source: adapted from the checklist in Ali et al., 2008)

3. THEORETICAL CONTEXT

3.1 Anatomicophysiological Description

The ear is composed of three parts: the outer ear, the middle ear and the inner ear. Figure 3 shows each of these parts. The outer ear consists of the pinna, or auricle, and the external auditory canal. The middle ear is separated from the outer ear by the eardrum, or tympanic membrane, a translucent membrane that vibrates when in contact with air molecules set in motion by sound. The vibrations of the eardrum are transmitted through a chain of ossicles (the malleus, incus and stapes) suspended inside a closed air-filled cavity. This cavity, the middle ear, and the structures that it contains (eardrum, ossicles) facilitate the passage of sound vibrations from the air environment, the ambient air, towards a liquid environment, the inner ear. The liquid environment of the inner ear holds the organs of hearing and balance. The part that resembles a snail is called the cochlea; it contains specialized sensorial cells for detecting sound energy. These cells enable the transduction of mechanical energy (vibrations in an air or liquid environment) into an assimilable electrical energy (action potential) by the central auditory system from nerve fibres that constitute the auditory nerve (Trottier, Leroux and Deadman, 2004).

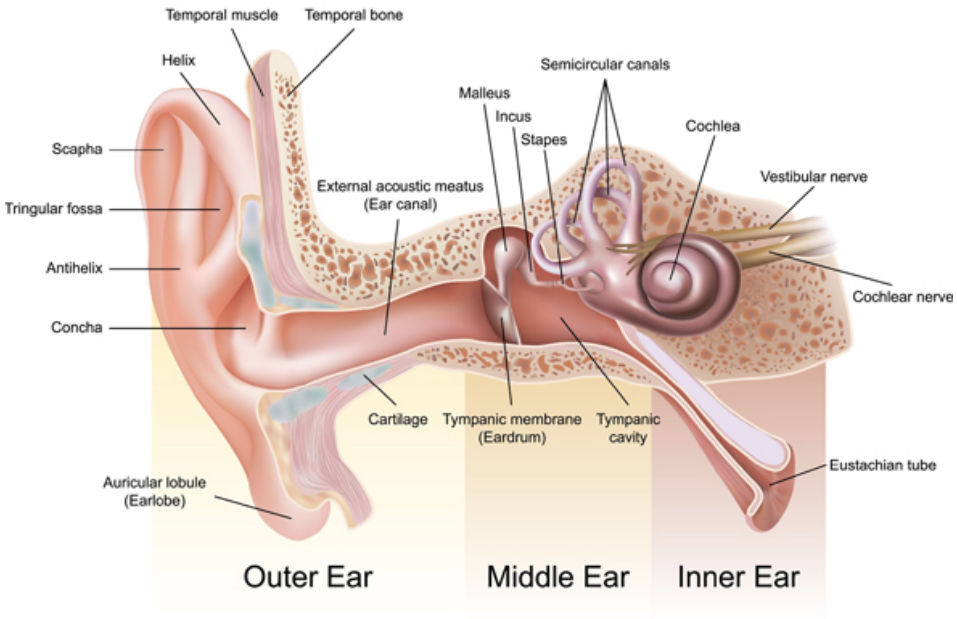


Figure 3 - Diagram of the ear.
(Source: http://www.audiologyspecialists.com/anatomy-of-the-ear/)

Figure 4 is a schematic illustration of the organization of the cells of the inner ear that form what is called the organ of Corti. In it are two types of sensory hair cells topped with finger-like projections (called stereocilia) bathed in the fluid contained in the inner ear. The inner hair cells (IHC) and outer hair cells (OHC) are separated by a space called the Tunnel of Corti, formed by support cells, such as Deiters cells, which support the OHC. The hair cells form synapses with the nerve fibres that constitute the auditory nerve. The two types of hair cells, while similar, have very different physical, anatomical and physiological characteristics.

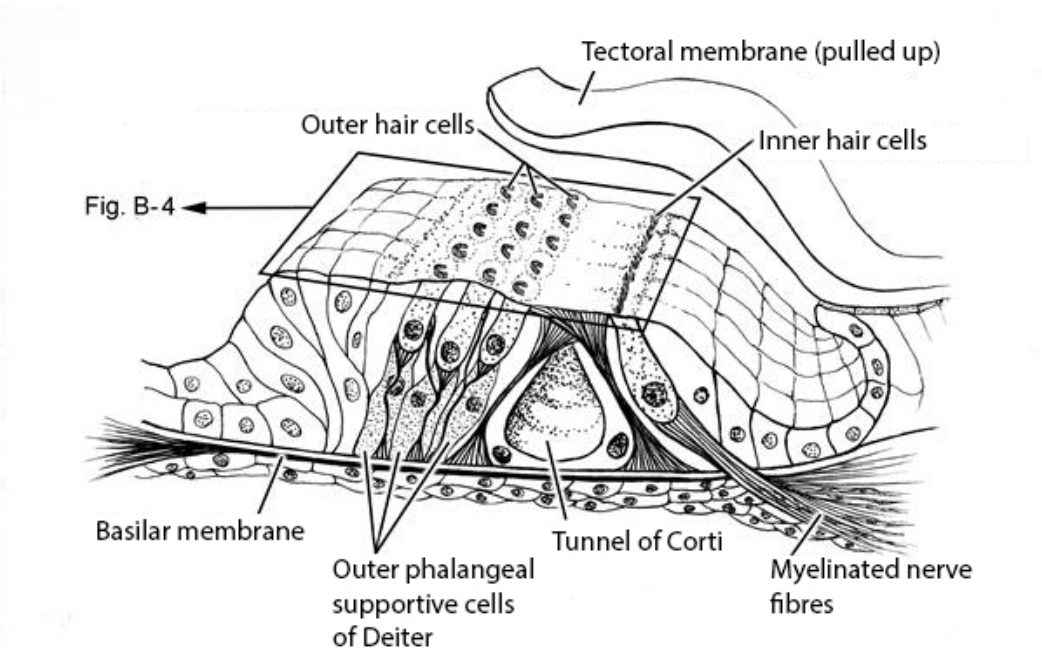


Figure 4 - Cross-sectional schematic view of the organ of Corti.
(Source : Rutka, 2013; Figure B-3, p. 34)

Table 2 summarizes the key differences observed between the OHC and the IHC. The organ of Corti rests on a flexible membrane, the basilar membrane, which moves in response to vibrations in the fluid of the internal ear. These two types of cells play specific and distinct roles: the motor activity of the OHC locally amplify the movement of the basilar membrane, thus contributing to the excitation of the IHC, which translate the mechanical energy by releasing neurotransmitters into the synapse, which will be captured by the receptors of the nerve fibres of the auditory nerve, thus generating action potentials that translate different characteristics of the sound stimulation (such as frequency, amplitude and duration) into an electrical code.

Table 2 - Main differences between the outer hair cells (OHC) and inner hair cells (IHC)

Characteristic	Outer hair cells (OHC)	Inner hair cells (IHC)
Number (human)	9000 to 12,500	3000 to 3500
Arrangement of cells	Three staggered rows	A single row
Form	Cylindrical	Pear-shaped
Structure	Cytoskeleton containing motor protein (prestin, actin) that enables the cell to change its size.	Conventional cytoskeleton
Arrangement of stereocilia	Three rows of Ws	Three aligned rows
Cellular organelles	Nucleus situated at the base of the cell (basal nuclei). Abundant mitochondria aligned along the cell body and below the basal nucleus.	Nucleus situated medially in the cell. Less abundant mitochondria than in the OHC and more uniformly organized in the cell body.
Neural network	Afferent system: synapses with small endings from non-myelinated type II spiral ganglia link the cochlea to cochlear nuclei (approximately 5% of auditory nerve fibres). Approximately ten OHC per type II neuron. Efferent system: very large descending endings from both sides of the medial superior olivary complex. The endings form axo-somatic synapses with the OHC cell body.	Afferent system: synapse with large myelinated type I spiral ganglion neurons, which link the cochlea to the cochlear nuclei (95% of auditory nerve fibres). 10 to 20 type I neurons per IHC. Efferent system: arising from small neurons in the ipsilateral lateral superior olivary complex bring feedback (post-synaptic) control to the type I afferent fibre
Type of synapse	Postsynaptic cistern	Presynaptic ribbon
Neurotransmitter	Aceylcholine, GABA, neuropeptide (descending fibres)	Glutamate (ascending fibres)
Functional role	Enables local amplification of the movements of the basilar membrane. Increases the sensitivity of the internal hair cells.	Enables transduction of mechanical energy into electrical energy. Actual sensory receptors.

The three rows of stereocilia situated at the top of each hair cell are attached to each other by tiny links: side links and tip links. The side links help to maintain cohesion among all of the stereocilia on a hair cell, while the first step of mechanical transduction originates in the tip links. The movement induced by the vibrations of the basilar membrane creates a shearing force that causes the stereocilia at the tips of the hair cells to bend. This stretches the tip links and opens potassium channels. The stereocilia are bathed in a fluid (endolymph) with a very high concentration of potassium, while the interior of the cell contains a much weaker concentration. The stretching of the tip links and the opening of the ionic canals leads to the massive influx of potassium into the cell, which depolarizes it.

In the case of the OHC, depolarization of the cells releases the neurotransmitter glutamate from presynaptic ribbons into the synaptic cleft (figure 5) (Fuchs, Glowatzki et Moser, 2003). This type of presynaptic structure enables a synchronized and rapid release of the neurotransmitter, faithfully reproducing the waves of a sound signal (Khimich et al., 2005). For the OHC, depolarization brings about changes in the configuration of the cytoskeleton, which amplifies the movements of the basilar membrane and increases the sensitivity of the IHC.

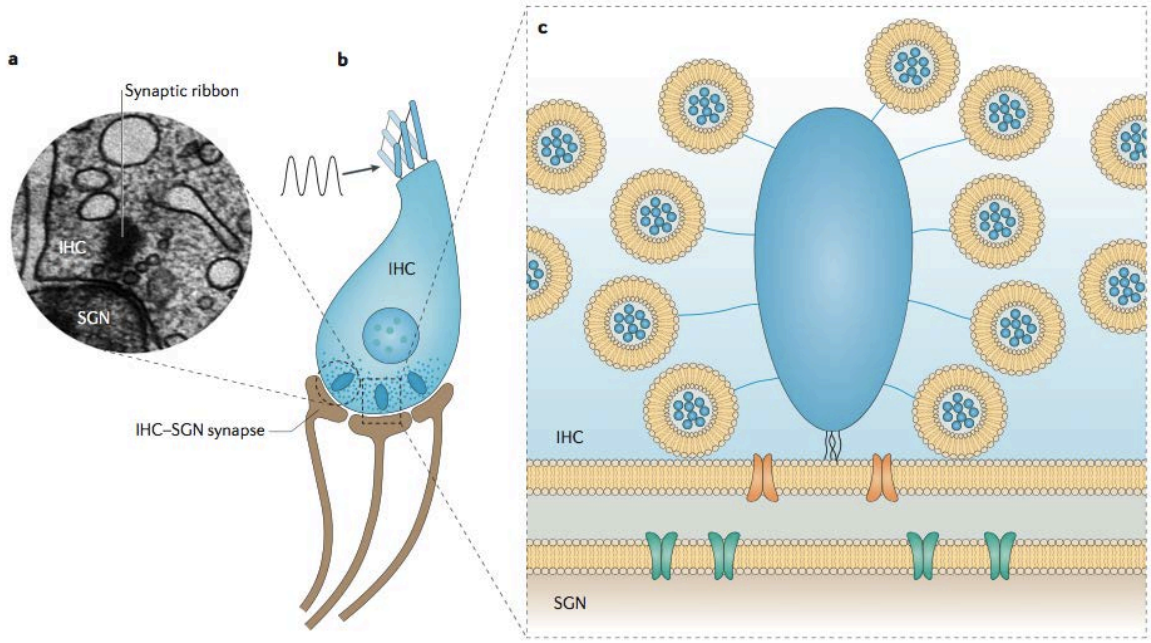


Figure 5 - Electron microscope view and schematic representation of the presynaptic ribbons of an IHC.
(Source : Moser and Starr, 2016)

There are at least three distinct populations of auditory neurons, characterized by their level of spontaneous activity (or rate), their sensitivity thresholds (the minimal sound level that will enable action potentials to be released), the organization of pre- and postsynaptic receptors and their position below the IHC. Figure 6 illustrates the anatomical characteristics of these three populations of neurons that establish a synapse with the IHC (at the left in the figure) and the corresponding electrophysiological responses (at the right in the figure). The neurons identified by the number ① (Figure 6), have a high spontaneous rate (high-SR; > 18 action potentials per second), illustrated in the figure by the presence of action potentials released despite the absence of stimulation (acoustic stimuli are identified by the orange elongated hexagons). The same neurons are activated by low sound levels, reflecting the capacity of the auditory system to detect low amplitude sounds. The discharge rate of these neurons saturates rapidly as amplitudes rise, in such a way that they code a range of approximately 20-30 dB (Bourien et al., 2014; Ruggero, 1992). Beyond 30 dB SPL, the discharge rate remains unchanged despite the increase in acoustic amplitude. These neurons also have a postsynaptic organization spread over a large surface and are most often situated on the side close to the Tunnel of Corti. The neurons identified by the number ③ (Figure 6) have, unlike those described previously, a low spontaneous rate (low SR; < 0.5 action potential per second) and emit a very low number of action potentials in the absence of sound stimulation. They are also not sensitive to low levels of sound stimulation and do not emit action potentials unless the amplitude is relatively high (over 60-80 dB SPL, on average) (Bourien et al., 2014; Ruggero, 1992). These neurons correspond to the ability to hear loud sounds (between 80 to 120 dB SPL). They also present with a more compact postsynaptic organization and are situated in greater numbers close to the modiolus. A third population of auditory neurons are positioned between the two populations previously described (medium SR, moderate release threshold, situated below the centre of the IHC, identified by the number ② in Figure 6).

Together, these three populations of neurons make it possible to code the entire dynamic range of hearing. In humans, at 1000 Hz, this dynamic range runs from 0 dB HL (perceptual threshold) to over 120 dB HL (pain threshold) (Zwicker and Fastl, 2013).

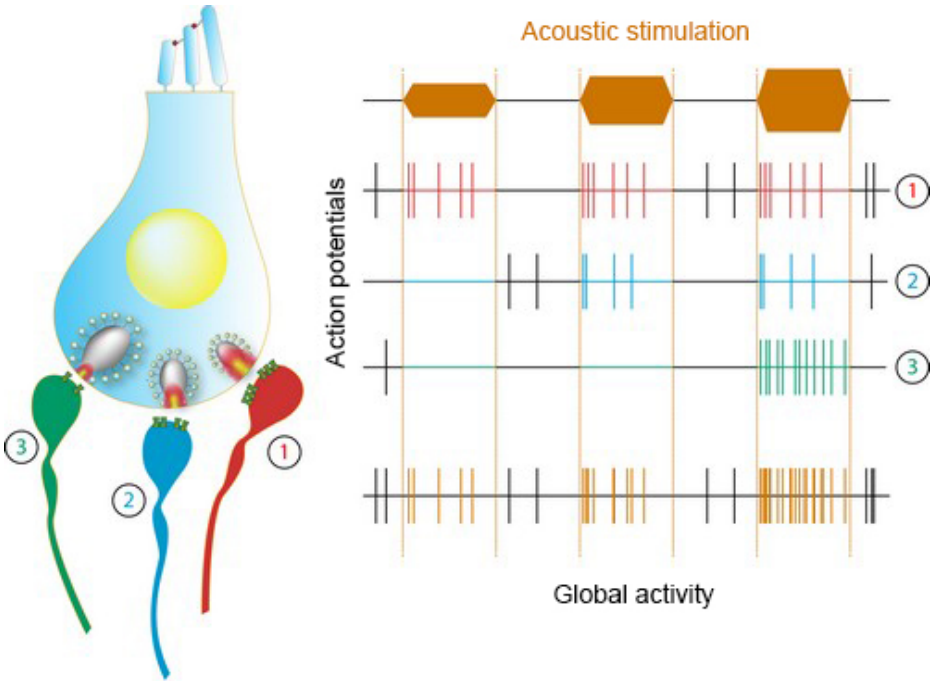


Figure 6 - Schematic illustration of three populations of neurons situated below the IHC.
(Source: Nouvian, 2016)

In the presence of moderate level of noise (60-80 dB SPL), the discharge rate of the medium-SR and high-SR neurons is saturated, so that coding of the characteristics of a sound signal presented in this sound environment is supported exclusively by the population of low-SR neurons (Costalupes, Young and Gibson, 1984).

3.2 Effects of Noise Exposure on the Inner Ear

Noise exposure also disturbs the functioning of the sensory cells of the inner ear (Bohne and Clark, 1982). If the level is sufficiently high, noise exposure initially provokes a temporary and reversible shift in hearing thresholds (TTS) (Clark, Bohne and Boettcher, 1987). After the exposure to noise ceases, the auditory system slowly and progressively recovers its initial hearing capacity. When the level of noise exposure is very high, the recovery of hearing thresholds can be incomplete, and when exposure is repeated over time, it can lead to a permanent and irreversible hearing threshold shift (PTS) (Bohne and Clark, 1982).

The classic histological description of the effects of TTS due to noise exposure shows, among others, the structural changes to the stereocilia of the hair cells (Robertson, Johnstone and McGill, 1980) (figure 7), particularly those of the OHC, and metabolic alterations (Meltser, Tahera and Canlon, 2010). The same classical histological description also shows that the

integrity of the sensorial cells is maintained and that their numbers, both for OHC and IHC, remain stable (Liberman and Mulroy, 1982). The recovery of hearing thresholds and the absence of structural damage would lead one to believe that a TTS is innocuous (Liberman et al., 2016).

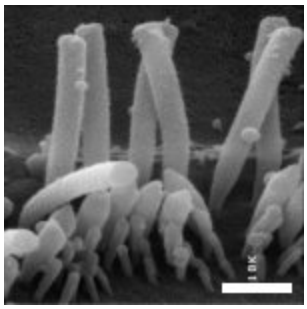


Figure 7 - Disorganization and reversible rupture of links between stereocilia (OHC; loss of side links).
(Source : Lenoir, 2013a)

When there is PTS caused by noise exposure, and depending on the severity of the exposure, the classical histological description shows destruction of stereocilia at the top of the hair cells (Liberman and Dodds, 1987) (Figure 8), a reduction in the number of hair cells, both IHC and OHC, but mainly the latter (Figure 9) (Liberman and Kiang, 1978), and destruction of the nerve fibres of the auditory nerve (Nordmann, Bohne and Harding, 2000). The destruction of nerve fibres of the auditory nerve occurs gradually over several weeks or months (in the animal model) compared to the rapid reduction of numbers of hair cells (Spoendlin, 1975). In the classical description, the degeneration of auditory nerve fibres is described as secondary to sensorineural degeneration (Johnsson, 1975).

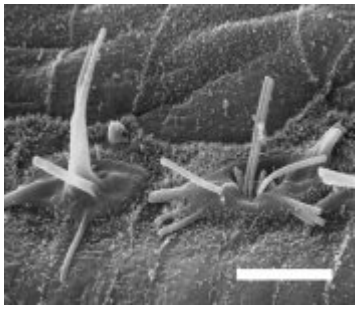


Figure 8 - Irreversible damage to stereocilia (OHC).
(Source : Lenoir, 2013a)

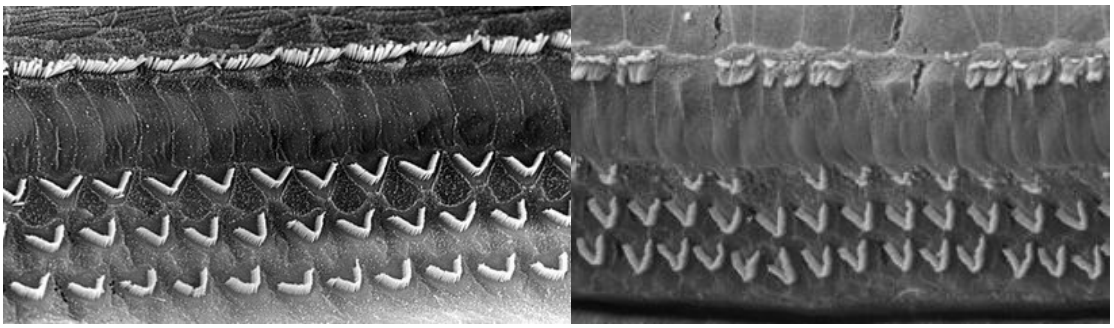


Figure 9 - Normal cochlea (left) and cochlea exposed to noise (right).
(Source : Lenoir, 2013b; Wang, 2016)

Clinically, tonal audiometry (hearing threshold measurement are transcribed on a graph called an audiogram) makes it possible to observe a permanent reduction in the ability of workers exposed to noise to detect high frequency sounds at low amplitudes, compared to what would be expected in a normal population that has not been exposed to noise. On the audiogram, this translates into a permanent shift of hearing thresholds situated between 3 and 6 kHz. The audiogram often shows a notch at the most affected frequency, while the auditory thresholds of the neighbouring frequencies, both the highest (> 6 kHz) and the lowest (< 3 kHz), remain within the limits of normal (see curve *a* in Figure 10). Over time, as the interval since the noise exposure lengthens, the degree of hearing loss gradually increases for frequencies between 3 and 6 3 and 6 kHz and the impairment slowly extends into the low frequencies (see curves *b-d* in Figure 10). After several years of noise exposure, the audiogram shows an impairment of hearing thresholds at high frequencies (≥ 2 kHz) with the severity being greater at the highest frequencies, while the sound thresholds at low frequencies (250 à 1000 Hz) remain about the same (see curves *e-f* in Figure 10).

The combined effect of exposure to noise and aging on the hearing thresholds of an otologically normal population of men and women is predicted by the ISO 1999:2013 standard (ISO, 2013). This standard predicts the statistical distribution (median and percentiles) of hearing thresholds (500 to 6000 Hz) for an otologically normal population of men and women according to age (18–80 years old, predicted with the ISO 7029:2017 standard),[2] how long it has been since the noise exposure occurred (≤ 40 years), and the daily level of noise exposure over an eight-hour period (≤ 100 dBA) (ISO, 2013). Developed using epidemiological data, the ISO 1999:2013 standard shows that daily exposure to a noise level of 75 dBA, eight hours a day, five days a week, 50 weeks a year for 40 years does not cause a permanent auditory threshold shift. It is therefore considered that a daily 8-hour long-term exposure to noise at a level of 75 dBA does not present a risk of hearing impairment.

[2] ISO 7029:2017 predicts the statistical distribution (median and percentiles) of hearing thresholds (125 to 12,500 Hz) in an otologically normal population of men and women according to age (18–80 years). This standard is commonly used to detect the presence of hearing loss that could be attributed to a cause other than aging.

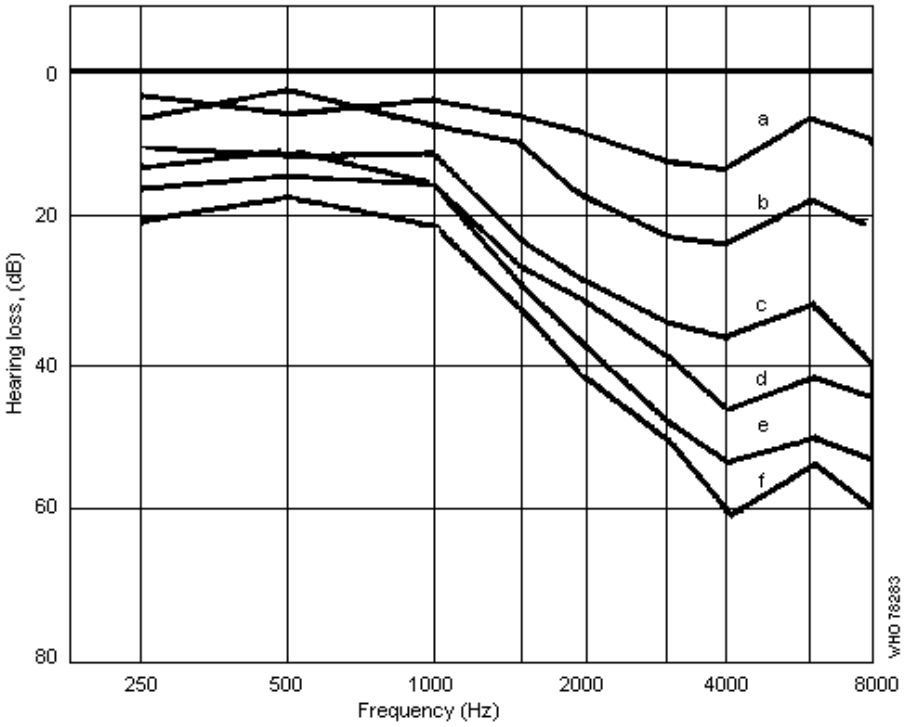


Fig. 3. Hearing loss as a function of number of years of noise exposure.
Mean audiograms for 203 miners, best ear tested.

a < 1 year
b 1 - 5 years
c 6 - 10 years
d 11 - 20 years
e 21 - 30 years
f > 30 years

(from: Johansson, 1952).

Figure 10 - Classic progression of hearing loss due to noise.
(Source : WHO, 1980)

Although they do not conflict with the classical physiopathologic description observed in the case of PTS, recent data raise doubts about the previously supposed harmlessness of noise exposure leading to TTS, as predicted by the ISO 1999:2013 standard (ISO, 2013), for example. The advance of histological techniques, including immunofluorescence, now make it possible to quantitatively examine the specific elements that make up the synapse at the base of the IHC (Liberman et al., 2016).

The studies by Furman et al. (2013) used this technique on an animal model (guinea pig). After a single exposure to noise that would be expected to produce a TTS (octave band noise 4–8 kHz, 106 dB SPL, 2 hours), followed by complete recovery of the composite action potential (linked to hearing thresholds), with no apparent alteration of the OHC, a permanent (almost 30%) and significant ($p<0.01$) decrease in the number of synapses below the IHC was observed

in the zone responding to the frequency of 32 kHz (Figure 11; panel B of the original Figure 3). Moreover, the numbers of pairs formed by presynaptic ribbons and postsynaptic receptors showed an approximately 5% reduction in the zone responding to the frequency of 16 kHz (Figure 11; panel C of the original Figure 3). Kujawa and Liberman (2009) refer to these morphological alterations provoked by noise exposure as synaptic loss.

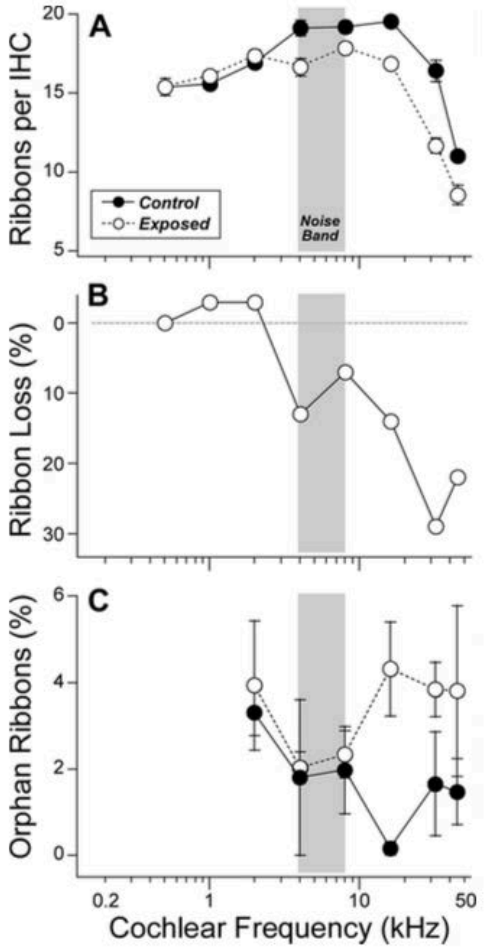


Figure 11 - Counts of IHC synaptic ribbons.
(Source : Furman et al., 2013; figure 3, p. 580)

Furman et al. (2013) also examined the neurons of the auditory nerve (the nuclei of which come together in a structure called the spiral ganglion, also referred to as spiral ganglion fibres) and noted the specific destruction of auditory neurons with low spontaneous rates (low-SR) presenting a broad dynamic range. Figure 12, from Furman et al. (2013), illustrates the specific disappearance of these neurons (identified by red triangles) not only in the portion of the cochlea exposed to noise, but over almost the entirety of the structure. Because these neurons are not involved in the coding of the amplitude of low-level sounds, their destruction does not affect hearing thresholds (measured by the auditory brainstem response), but limits coding of the amplitude of high-level sounds.

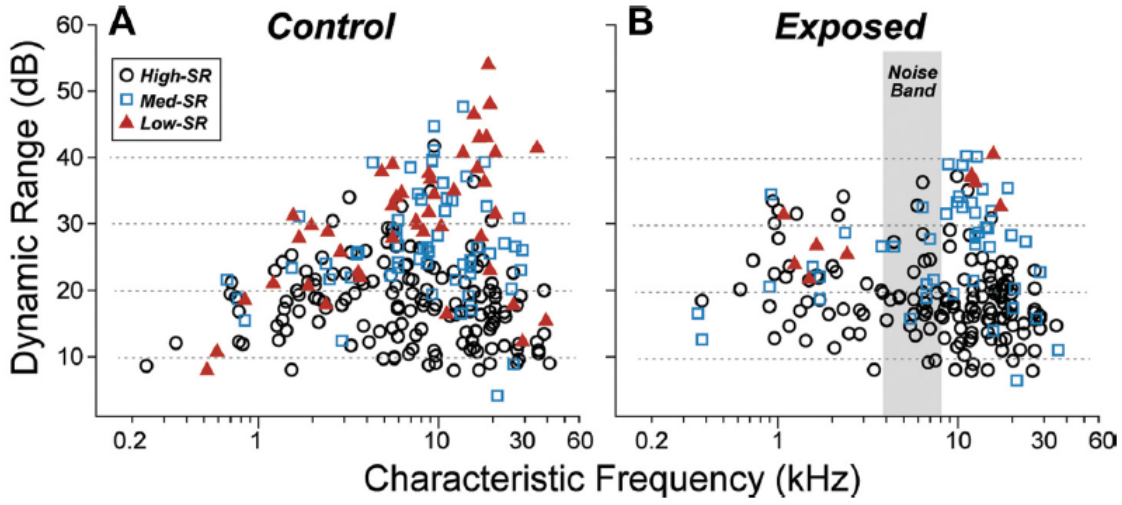


Figure 12 - Count of a guinea pig's type I auditory fibres, according to spontaneous discharge rate [High-SR, Med-SR and Low-SR] and the dynamic range.
(Source : Furman et al., 2013; extract from figure 6, p. 582)

Figure 13, also from Furman et al. (2013), illustrates that the electrophysiological thresholds of the auditory brainstem response (ABR; panel A) are negligibly affected by exposure to noise, while the increase in wave I amplitude of this auditory brainstem response (panel C) is abnormally weak at a high sound pressure level among the group of exposed guinea pigs, despite the integrity of the OHC, as demonstrated by identical otoacoustic emissions (DPOAE) for the control group and the noise-exposed group (panels B and D). This auditory dysfunction, despite the presence of normal hearing thresholds, is referred to as “hidden hearing loss” due to noise, first suggested by Schaette and McAlpine (2011).

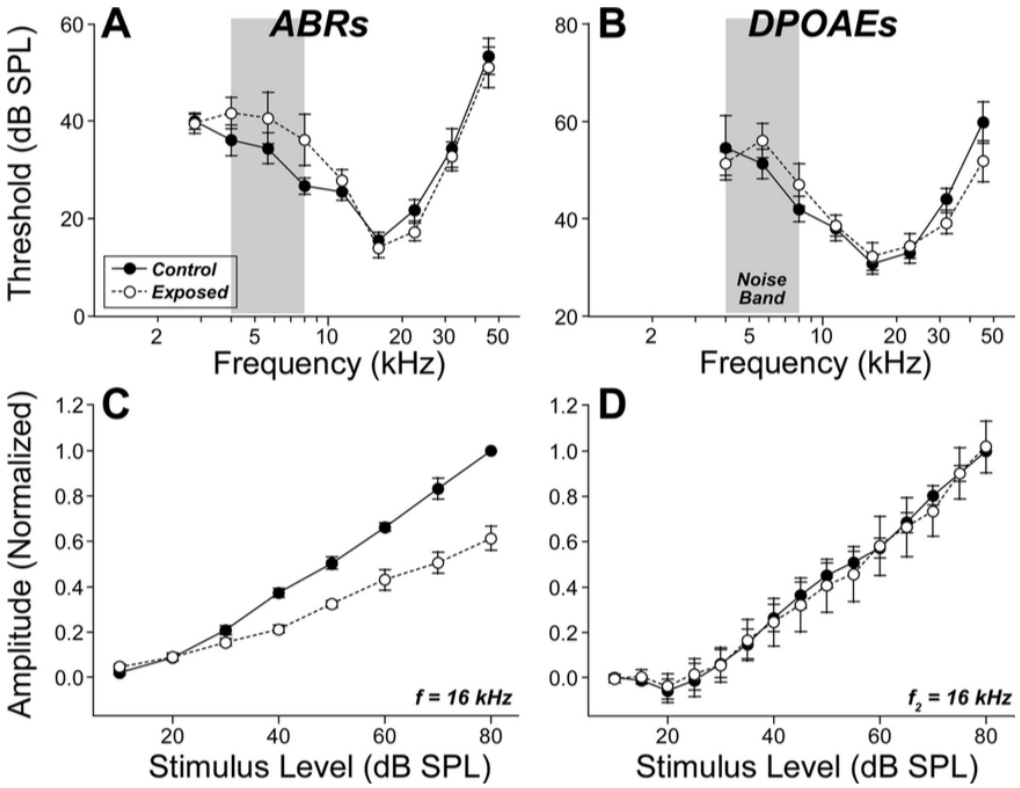


Figure 13 - Auditory brainstem response (ABR) and distortion product otoacoustic emissions (DPOAE) pre- and post-exposure to noise in guinea pigs (n=9).
(Source : Furman et al., 2013; figure 1, p. 579)

Figure 14, from Shi et al. (2016), combines the contemporary explanatory models (model 1 on the left, permanent destruction of low-SR fibres of the auditory nerve; model 2 on the right, an inadequate repair of synapses under the IHC) that are the basis of the auditory dysfunction observed in the presence of a synaptopathy provoked by noise exposure. While the hearing thresholds are not affected by the selective destruction of low-SR auditory neurons, other aspects of auditory function show abnormal characteristics in terms of coding of the amplitude and temporal information.

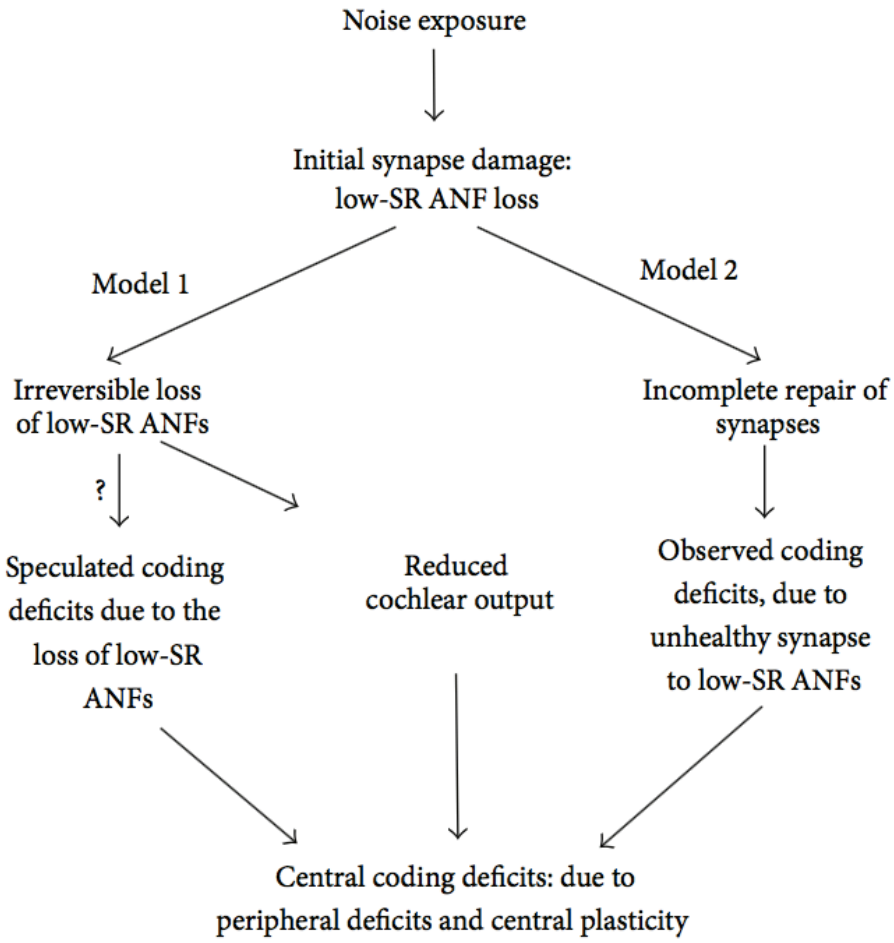


Figure 14 - Models explaining auditory dysfunction observed following noise exposure causing synaptopathy.
(Source : Shi et al., 2016; figure 2, p. 5)

Figure 15, from Meija et al. (2015), shows hypothesized relationships among the injury sites attributable to noise exposure, as highlighted by the work of the Harvard University team (Kujawa and Liberman), and electrophysiological (auditory brainstem response [ABR]) and behavioural (psychoacoustic tests to detect amplitude modulation, AM threshold) clinical trials. An examination of the components in this figure shows that the audiogram, which is the foundation of current assessments of the effects of noise on hearing, is not affected by the primary effects of this exposure on the synapses found on the IHC and the degeneration observed in the low-SR fibres of the auditory nerve, although the impairment causes significant problems in understanding speech in a noisy environment.

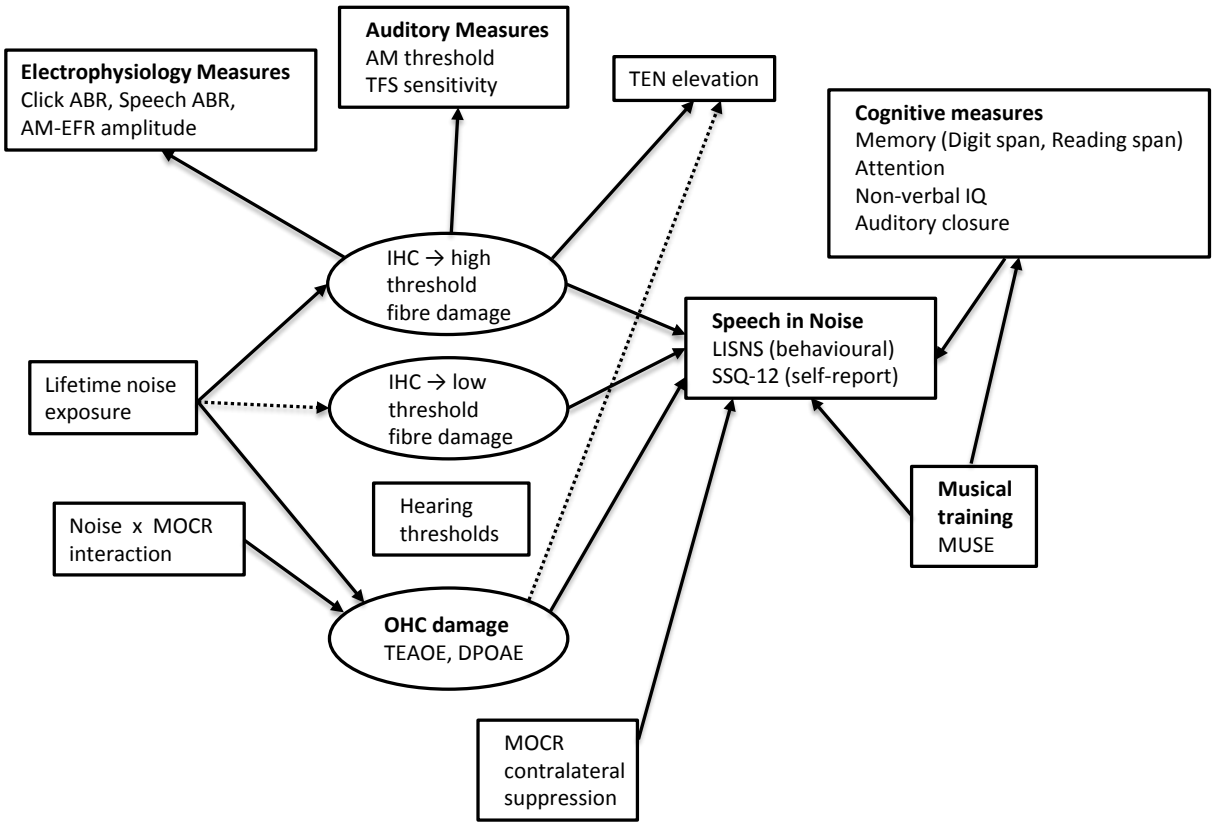


Figure 15 - Illustration of the effects of noise exposure on various populations of auditory neurons and the electrophysiological and the psychoacoustic tests that bring them to light.

(Source : Meija et al., 2015; figure 1, p. 207)

3.3 Effects of Aging on the Inner Ear

Aging, like noise exposure, is associated with progressive degradation of hearing thresholds. This hearing loss, called presbycusis, is pathophysiologically associated with changes in the functioning of the sensory cells of the inner ear, the stria vascularis, the nerve fibres of the auditory nerve, the spiral ganglion and the structures of the central auditory system (Yamasoba et al., 2013). There is likely not a single cause of presbycusis (Gates and Mills, 2005; Wong and Ryan, 2015). It is, instead, probably an interaction of intrinsic (gender, mitochondrial DNA mutations, genetic diseases and disorders, systemic diseases, high blood pressure, and metabolic diseases such as diabetes) and extrinsic (noise exposure, consumption of ototoxic medication, smoking, diet, exposure to pollutants, etc.) (Tavanai and Mohammadkhani, 2017; Yamasoba et al., 2013; Wong and Ryan, 2015) causes.

Based on a histological analysis of human temporal bones, Schuknecht (1955) proposed a classification of four types of presbycusis by linking the audiometric profile to an injury site in the auditory system. *Sensory* presbycusis is hearing loss that seriously affects hearing thresholds at high frequencies and is associated with a decrease in the number of hair cells in the inner ear. *Neural* presbycusis is hearing loss that affects hearing thresholds at high frequencies and is associated with a decrease in the number of nerve cells in the spiral ganglion. *Metabolic* or *stria* presbycusis is hearing loss that affects the hearing thresholds at every frequency equally and is associated with atrophy of the stria vascularis. *Mechanical* or *conductive* presbycusis is associated with progressive rigidity of the basilar membrane. This latter type of presbycusis is theoretical and does not result from histological observation (Gates and Mills, 2005). In 1993, Schuknecht and Gacek added two new types, *mixed* presbycusis and *indeterminate* presbycusis.

The evolution of knowledge and a re-evaluation of the collection of temporal bones used by Schuknecht has revealed that the specimens in which he had identified sensory presbycusis, involving a decrease in the number of hair cells in the inner ear, were from men who had all been exposed to noise throughout their life. For Gates and Mills (2005), the sensory presbycusis identified by Schuknecht was, in fact, hearing impairment due to noise exposure and had nothing to do with aging.

Stria presbycusis is the type of presbycusis found most frequently in the population and appears to most directly reflect the phenomenon of aging when the influence of noise exposure is controlled (Gates and Mills, 2005; Kurata et al., 2016; Schuknecht and Gacek, 1993; Yamasoba et al., 2013). In a study carried out in 1990, Mills et al. examined changes in hearing thresholds in gerbils raised in silence. These animals showed progressive impairment to hearing thresholds at every frequency, both high and low, and atrophy of the stria vascularis. Similar results were also obtained by Sergeyenko, Lall, Liberman and Kujawa (2013) in old mice that had not been exposed to noise.

At the molecular level, the production of free radicals (or reactive oxygen species, ROS) appear key to the physiopathologic process associated with hearing loss due to aging (Tavanai and Mohammadkhani, 2017; Wong and Ryan, 2015; Yamasoba et al., 2013). As illustrated in Figure 16, a number of intrinsic and extrinsic factors (in particular, noise exposure) have in common

the production of free radicals. Under certain conditions, free radicals set off an oxidative process that affects the lipid and protein structures of cells and leads to mutations of mitochondrial DNA. These alterations can trigger the apoptotic response (programmed cell death) in the hair cells of the inner ear, the cells of the stria vascularis, the nerve fibres of the spiral ganglion and the fibres that constitute the various circuits of the central hearing system. Possibly resulting from a common process, through a cascade of oxidative damage, the death of different types of cells in the auditory system can explain the multidimensional nature of hearing loss observed with aging (Wong and Ryan, 2015). The multidimensional nature would also be in line with the observations of Schuknecht and Gacek (1993), who have identified several sites of impairment of the auditory system in mixed presbycusis.

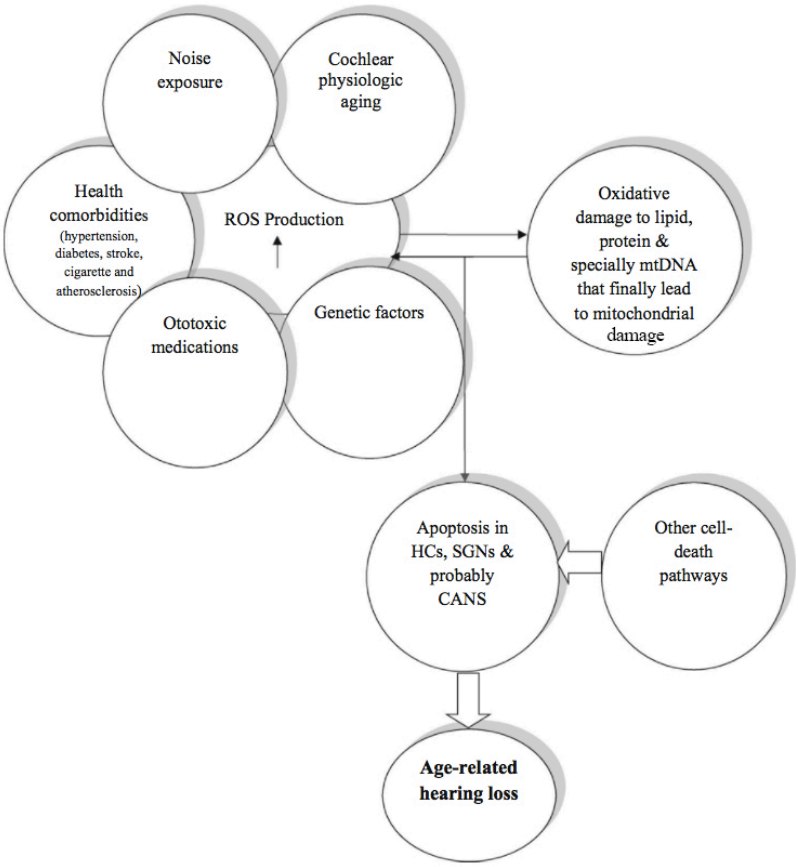
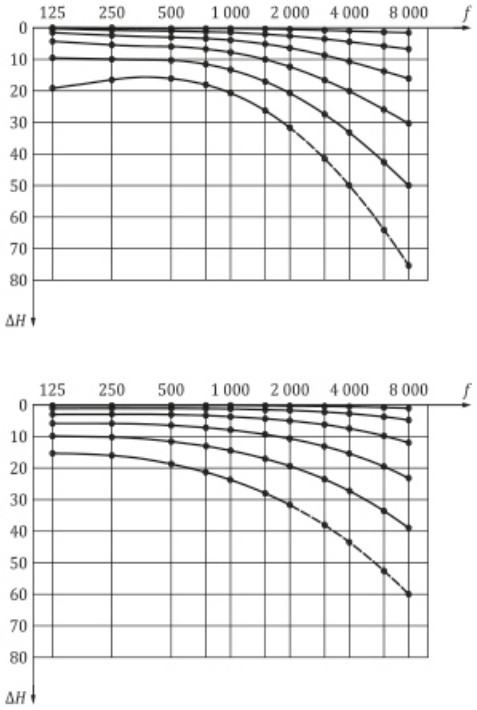


Figure 16 - Explanatory model proposed to explain hearing loss due to aging.
(Source : Tavanai et Mohammadkhani, 2017; figure 1, p. 1822)

Clinically, presbycusis is most often described as a progressive decrease in hearing thresholds that first affect the higher frequencies, and then progressively spread to the lower frequencies. The ISO 7029:2017 standard predicts statistical distribution (median and percentiles) of hearing thresholds (125 to 12 500 Hz) for an otologically normal population of men and women according to age (18-80 years) (ISO, 2017). Figure 17 illustrates the median values of hearing

thresholds from 125 to 8000 Hz for an otologically normal population of men (upper graph and women (lower graph) for each decade from 30 to 80 years. We note that degradation of the hearing thresholds is greater and occurs more rapidly in men than in women.



Key

f frequency, Hz

ΔH hearing threshold deviation, dB

From top to bottom, the curves represent $\Delta H_{\mathrm{md},Y}$ values when Y is 30 years, 40 years, 50 years, 60 years, 70 years or 80 years.

NOTE 1 The dashed portion of the curve of $\Delta H_{\mathrm{md},Y}$, $Y = 80$, is presented for informative purposes only.

NOTE 2 The $\Delta H_{\mathrm{md},80}$ values at 125 Hz are liable to a large uncertainty of estimation because of the scarcity of source data.

Figure C.1 — Median values of expected hearing threshold deviation for males (upper panel) and females (lower panel)

Figure 17 - Median values of hearing thresholds shift attributable to age.

(Source : norme ISO 7029:2017; figure C.1, p. 9)

The difference observed between men and women suggests that age and aging are not the only causes of presbycusis. As mentioned previously, the contemporary concept of presbycusis implicates factors that are intrinsic and extrinsic to the individual. Exposure to noise is one of the most frequent extrinsic factors in populations. We also note that men are more likely to be socially exposed to noise (Glorig and Nixon, 1962). One may therefore suspect that the values provided in the ISO 7029:2017 standard are tainted by the effect of social exposure to noise,

which adds to the intrinsic factors found in a population (Wong and Ryan, 2015). Old studies conducted with preindustrial populations have shown that men in those societies had hearing thresholds that were significantly better than those living in industrialized societies (Bergman, 1966; Goycoolea et al., 1986; Rosen et al., 1962). Using contemporary knowledge, it could be hypothesized that the process of synaptopathy associated with noise exposure may explain, at least in part, the slow degradation of hearing thresholds with age and the difference observed between men and women (Yamasoba et al., 2013).

4. NOISE EXPOSURE AND PRESBYCUSIS

The first question asked by the IRSST sought to establish the link between noise exposure and presbycusis. It was formulated as follows: Can noise exposure accelerate the process of presbycusis?

This question will be addressed by looking at animal and human studies that have considered the potential influence of the cochlear synaptopathy process described in the previous section (Kujawa and Liberman, 2006). While it has been clearly demonstrated that normal hearing thresholds do not necessarily indicate the absence of auditory synaptopathy either due to noise exposure or aging (Shi et al., 2016), this section will also analyze the results of studies that used only audiometric data to respond to the question. Twenty-eight articles dealing with the effects of the interaction of noise exposure and normal aging on hearing capacity were identified. The findings from the animal studies are presented first, followed by those from the human studies.

4.1 Animal Studies

Fourteen of the 28 articles are based on animal studies (tables 3 and 4), most of which are controlled studies (12/14; 85.7%), one is a randomized controlled trial (1/14; 7.1%), and the other is a time series (1/14; 7.1%). On average, the 14 animal studies underwent a quality assessment, obtaining 10.9/14 points, which places this corpus in the category of high quality studies (Ali, Suebwongpat and Weston, 2008). In addition, the experimental designs used to conduct these studies are almost all situated at level III-2, which provides a weight of evidence that is quite strong (Merlin et al., 2009). Appendix 3 presents the results of the quality assessment process of all the articles retained for analysis.

Table 3 - Summary of animal studies dealing with presbycusis

PRESBYCUSIS (SYNAPTOPATHY)				
Number of articles = 9				
Reference	**Type of study**	**Level of evidence**	**Quality assessment (/14 pts.)**	**Sample size (n)**
Campo, P., Venet, T., Rumeau, C., Thomas, A., Rieger, B., Cour, C. and Parietti-Winkler, C. (2011). Impact of Noise or Styrene Exposure on the Kinetics of Presbycusis. *Hearing Research*, 280(1), 122-132.	Controlled study	III-2	11	140
Fernandez, K. A., Jeffers, P. W., Lall, K., Liberman, M. C. and Kujawa, S. G. (2015). Aging After Noise Exposure: Acceleration of Cochlear Synaptopathy in "Recovered" Ears. *The Journal of Neuroscience*, 35(19), 7509-7520.	Controlled study	III-2	11	65
Gannouni, N. et al. (2015). Cochlear Neuropathy in The Rat Exposed for a Long Period to Moderate-Intensity Noises. *The Journal of Neuroscience Research*, 93(6): 848-858.	Controlled study	III-2	11	12
Gleich, O., Semmler, P. and Strutz, J. (2016). Behavioral auditory thresholds and loss of ribbon synapses at inner hair cells in aged gerbils. *Experimental Gerontology*, *84*, 61-70.	Controlled study	III-2	11	14
Jensen, J. B., Lysaght, A. C., Liberman, M. C., Qvortrup, K. and Stankovic, K. M. (2015). Immediate and Delayed Cochlear Neuropathy After Noise Exposure in Pubescent Mice. *PloS One*, 10(5), e0125160.	Controlled study	III-2	11	142
Kujawa, S. G. and Liberman, M. C. (2006). Acceleration of Age-Related Hearing Loss by Early Noise Exposure: Evidence of a Misspent Youth. *The Journal of Neuroscience*, 26(7): 2115-2123.	Controlled study	III-2	10	354
Sergeyenko, Y., Lall, K., Liberman, M. C. and Kujawa, S. G. (2013). Age-Related Cochlear Synaptopathy: An Early-Onset Contributor to Auditory Functional Decline. *The Journal of Neuroscience*, 33(34), 13686-13694.	Time series	III-2	10	120
Song, Q., Shen, P., Li, X., Shi, L., Liu, L., Wang, J. and Wang, J. (2016). Coding Deficits in Hidden Hearing Loss Induced by Noise: The Nature and Impacts. *Scientific Reports*, 6.	Controlled study	III-2	11	64
Wang, Y. and Ren, C. (2012). Effects of Repeated "Benign" Noise Exposures in Young CBA Mice: Shedding Light on Age-Related Hearing Loss. *Journal of the Association for Research in Otolaryngology*, 13(4), 505-515.	Randomized controlled trial	II	12	81
			Mean = 10.9 pts.	

Table 4 - Summary of animal studies dealing with noise exposure

NOISE EXPOSURE (SYNAPTOPATHY)				
Number of articles = 12				
Reference	**Type of study**	**Level of evidence**	**Quality assessment (/14 pts.)**	**Sample size (n)**
Campo, P., Venet, T., Rumeau, C., Thomas, A., Rieger, B., Cour, C., and Parietti-Winkler, C. (2011). Impact of Noise or Styrene Exposure on the Kinetics of Presbycusis. *Hearing Research*, 280(1), 122-132.	Controlled study	III-2	11	140
Fernandez, K. A., Jeffers, P. W., Lall, K., Liberman, M. C. and Kujawa, S. G. (2015). Aging After Noise Exposure: Acceleration of Cochlear Synaptopathy in "Recovered" Ears. *The Journal of Neuroscience*, 35(19), 7509-7520.	Controlled study	III-2	11	65
Furman, A. C., Kujawa, S. G. and Liberman, M. C. (2013). Noise-Induced Cochlear Neuropathy Is Selective for Fibres With Low Spontaneous Rates. *Journal of Neurophysiology*, 110(3), 577-586.	Controlled study	III-2	11	23
Gannouni, N. et al. (2015). Cochlear Neuropathy in The Rat Exposed for a Long Period to Moderate-Intensity Noises. *The Journal of Neuroscience Research*, 93(6): 848-858.	Controlled study	III-2	11	12
Jensen, J. B., Lysaght, A. C., Liberman, M. C., Qvortrup, K., and Stankovic, K. M. (2015). Immediate and Delayed Cochlear Neuropathy After Noise Exposure in Pubescent Mice. *PloS One*, 10(5), e0125160.	Controlled study	III-2	11	142
Kujawa, S. G. and Liberman, M. C. (2006). Acceleration of Age-Related Hearing Loss by Early Noise Exposure: Evidence of a Misspent Youth. *The Journal of Neuroscience*, 26(7): 2115-2123.	Controlled study	III-2	10	354
Kujawa, S. G. and Liberman, M. C. (2009). "Adding Insult to Injury: Cochlear Nerve Degeneration After 'Temporary' Noise-Induced Hearing Loss." *The Journal of Neuroscience*, 29(45), 14077-14085.	Controlled study	III-2	10	28
Lin, H. W., Furman, A. C., Kujawa, S. G. and Liberman, M. C. (2011). Primary neural degeneration in the Guinea pig cochlea after reversible noise-induced threshold shift. *Journal of the Association for Research in Otolaryngology*, *12*(5), 605-616.	Controlled study	III-2	11	30
Maison, S.F., Usubuchi, H. and Liberman, M.C. (2013). Efferent feedback minimizes cochlear neuropathy from moderate noise exposure. *J. Neurosci. 33, 5542-5552.*	Controlled study	III-2	11	27
Mehraei, G., Hickox, A. E., Bharadwaj, H. M., Goldberg, H., Verhulst, S., Liberman, M. C., and Shinn-Cunningham, B. G. (2016). Auditory Brainstem Response Latency in Noise as a Marker of Cochlear Synaptopathy. *The Journal of Neuroscience*, *36*(13), 3755-3764.	Controlled study	III-2	12	63

Song, Q., Shen, P., Li, X., Shi, L., Liu, L., Wang, J., and Wang, J. (2016). Coding Deficits in Hidden Hearing Loss Induced by Noise: The Nature and Impacts. *Scientific Reports*, 6.	Controlled study	III-2	11	64
Wang, Y. and Ren, C. (2012). Effects of Repeated "Benign" Noise Exposures in Young CBA Mice: Shedding Light on Age-Related Hearing Loss. *Journal of the Association for Research in Otolaryngology*, 13(4), 505-515.	Randomized controlled trial	II	12	81
			Mean = 11.0 pts.	

The principal conclusions that can be drawn from the studies conducted with animal models (guinea pig, mouse, rat) are that moderate to high noise exposure (70–85 to 90–100 dB SPL) can trigger the synaptopathy process (Fernandez, Jeffers, Lall, Liberman and Kujawa, 2015; Gannouni et al., 2015; Jensen, Lysaght, Liberman, Qvortrup and Stankovic, 2015; Kujawa and Liberman, 2009; Lin, Furman, Kujawa and Liberman, 2011; Maison, Usubuchi and Liberman, 2013; Mehraei et al., 2016; Song et al., 2016; Wang and Ren, 2012). This process starts after a TTS, and despite total recovery from it, we observe, depending on the previous exposure level, a rapid and permanent destruction of a significant proportion (>40%) of the presynaptic ribbons of the IHC. Figure 18, taken from Kujawa and Liberman (2009), illustrates the permanent loss observed in mice of the number of synaptic ribbons found on an IHC after a single exposure to noise (100 dB SPL, 2 hours, octave band noise 8–6 kHz).

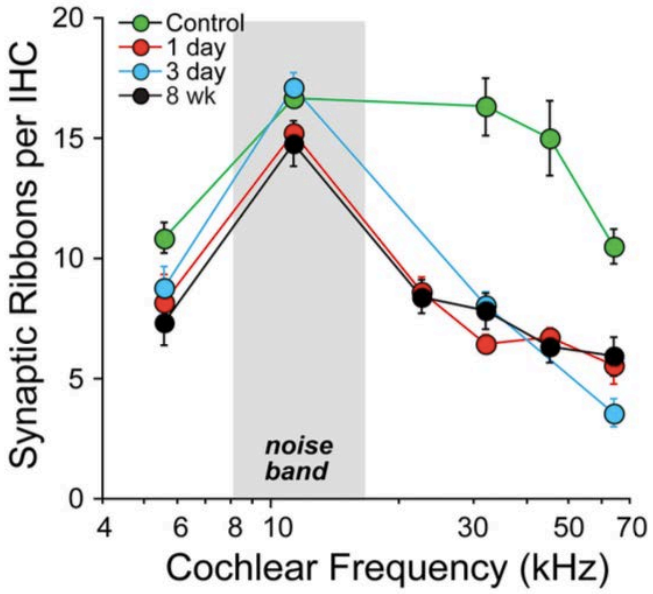


Figure 18 - Effects of noise exposure on the number of synaptic ribbons per IHC.
(Source : Kujawa and Liberman, 2009; figure 7, p. 19)

The synaptic ribbons in contact with the fibres of the spiral ganglion with low-SR activity appear to be the most vulnerable (Furman et al., 2013; Jensen et al., 2015; Kujawa and Liberman, 2009; Lin et al., 2011; Song et al., 2016). This destruction does not affect hearing thresholds (in animals, measured from an electrophysiological equivalent such as the brainstem auditory

evoked potential), nor the integrity of OHC measured using autoacoustic emissions (Fernandez et al., 2015; Furman et al., 2013; Jensen et al., 2015; Kujawa and Liberman, 2009; Maison et al., 2013; Mehraei et al., 2016; Song et al., 2016; Wang and Ren, 2012). The destruction of the presynaptic ribbons spreads progressively to the IHC situated near the apex of the cochlea, gradually affecting lower frequencies (Fernandez et al., 2015; Jensen et al., 2015). When compared with animals of the same age that have not been exposed to noise, we note, in the latter, less of a drop in the number of presynaptic ribbons (25 to 40% more presynaptic ribbons in this group, depending on the area of the cochlea being analyzed) and a later onset of this process (Fernandez et al., 2015; Jensen et al., 2015). When the groups of young and old animals that have not been exposed to noise are compared, we note an age-related reduction in the number of synaptic ribbons (Gleich, Semmler and Strutz, 2016). In gerbils, this reduction is, however, greater at the apex of the cochlea (38%) than at the base (16%) (Gleich et al., 2016). Figure 19, from Fernandez et al. (2015), illustrates the acceleration provoked by the synaptopathy triggered by noise exposure compared to the effect of normal aging in mice. We observe in panels C and D, the rapid (one hour post-exposure) and permanent disappearance of synapses found below the IHC, corresponding to the zone of the cochlea the most affected by noise exposure (22.6 and 32 kHz).

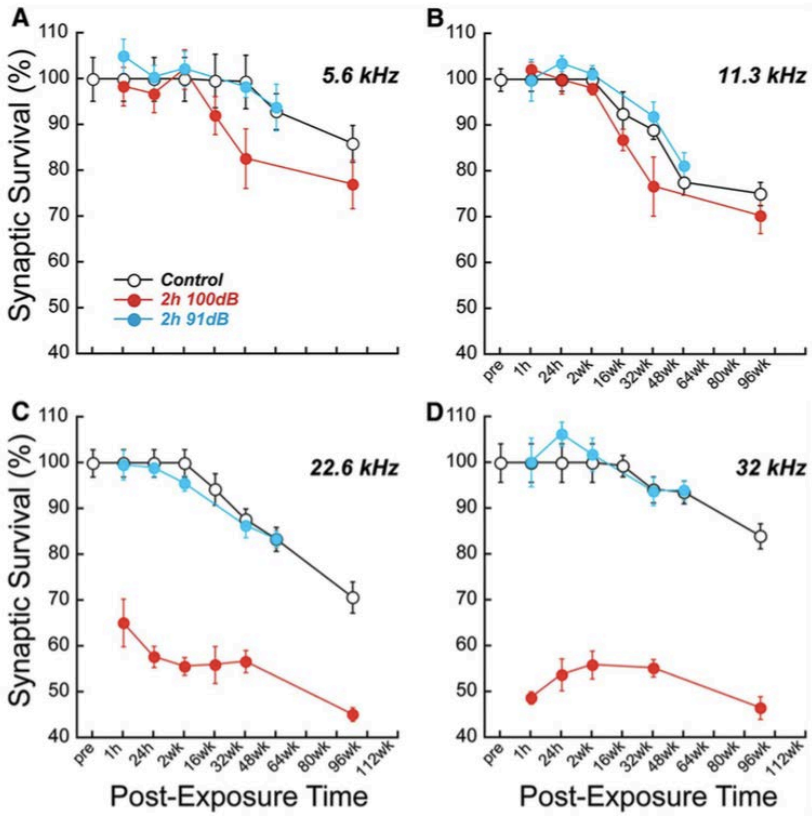


Figure 19 - Effect of noise exposure and normal aging in the survival rate of synapses below the IHC, in mice.

(Source : Fernandez et al., 2015; figure 3, p. 7513)

The amplitude of the TTS appears to influence the triggering of the synaptopathy process (Fernandez et al., 2015; Mehraei et al., 2016). In other words, exposure to noise can lead to a TTS without alterations to presynaptic ribbons being detected (Fernandez et al., 2015; Mehraei et al., 2016). Noise exposure of 84 dB SPL for one week, leading to a TTS of 15 dB that recovers very quickly, is enough to destroy approximately 20% of the presynaptic ribbons in the cochlear zone corresponding to the noise spectrum used during the sound exposure (Maison et al., 2013). In addition, contrary to the equal-energy rule that makes it possible to predict the changes in magnitude of a TTS according to the intensity of the exposure (Burns and Robinson, 1970), the extent of destruction of the presynaptic ribbons, especially those linked to the fibres of the spiral ganglion with low-SR activity, can vary from 0 to 50%, for a 3 dB increase in the intensity of the stimulation (Jensen et al., 2015). Song et al. (2016) showed that, for guinea pigs, contrary to what has been observed in mice and rats, in one group, there was a partial recovery in the number of presynaptic ribbons one week later, and in another group, recovery occurred one month after noise exposure ceased. The same authors reported, however, that the characteristic responses of the fibres with low-SR activity forming synapses with these "regenerated" presynaptic ribbons show abnormalities in the temporal coding of auditory information.

The sudden destruction of synaptic ribbons and the delayed process of degeneration of the same structures in other parts of the cochlea is also accompanied by the slow and progressive destruction, over time, of the fibres of the spiral ganglion on that constitute the auditory nerve. This degeneration, which was not observed in the short term in animal models, appeared several months and even several years after cessation of noise exposure and the sudden onset of synaptopathy (Campo et al., 2011; Fernandez et al., 2015; Gannouni et al., 2015; Jensen et al., 2015; Kujawa and Liberman, 2006). In old animals that were not exposed to noise, we note that there is no acceleration in the loss of spiral ganglion fibres until the animal has reached 80% of its lifespan, while it appears earlier in animals exposed to noise (Sergeyenko, Lall, Liberman and Kujawa, 2013) and the impact is magnified (Campo et al., 2011). Figure 20, from Kujawa and Liberman (2006), shows that animals that were exposed to noise from their fifth week of life (but tested at 100 weeks) presented with a greater loss of spiral ganglion on cells in all the sections of the cochlea, but most significant at the base and in the centre, compared to animals that were not exposed to noise and tested in their 105th week of life.[3] The disparity observed between animals exposed to noise and those that were not increases with age, with animals exposed to noise presenting with a more rapid loss of numbers of fibres (Campo et al., 2011). The fibres of the spiral ganglion with low-SR activity are more vulnerable and show a greater loss than other fibres (Furman et al., 2013). Degeneration of this type of fibre moves more rapidly toward complete destruction and is thus less subject to the effect of aging (Furman et al., 2013). There appears to be less degeneration of spiral ganglion fibres among guinea pigs, because the destroyed presynaptic ribbons regenerate partially, which maintains contact between the fibres, thus influencing their integrity (Song et al., 2016).

[3] The panel identified as "*Unexposed Test Old*" in Figure 20 shows a greater decrease in external hair cells and spiral ganglion cells at the apex of the cochlea, compared to the "Expose Old Test Old" group for the equivalent section of the cochlea. Kujawa and Liberman (2006) explain this counter-intuitive result by a trait in the strain of mice used (CBA/CaJ) for the study, which randomly presents with alterations of that nature when the animal ages. The trait has also been reported by other authors (see page 2119, in Kujawa and Liberman (2006)).

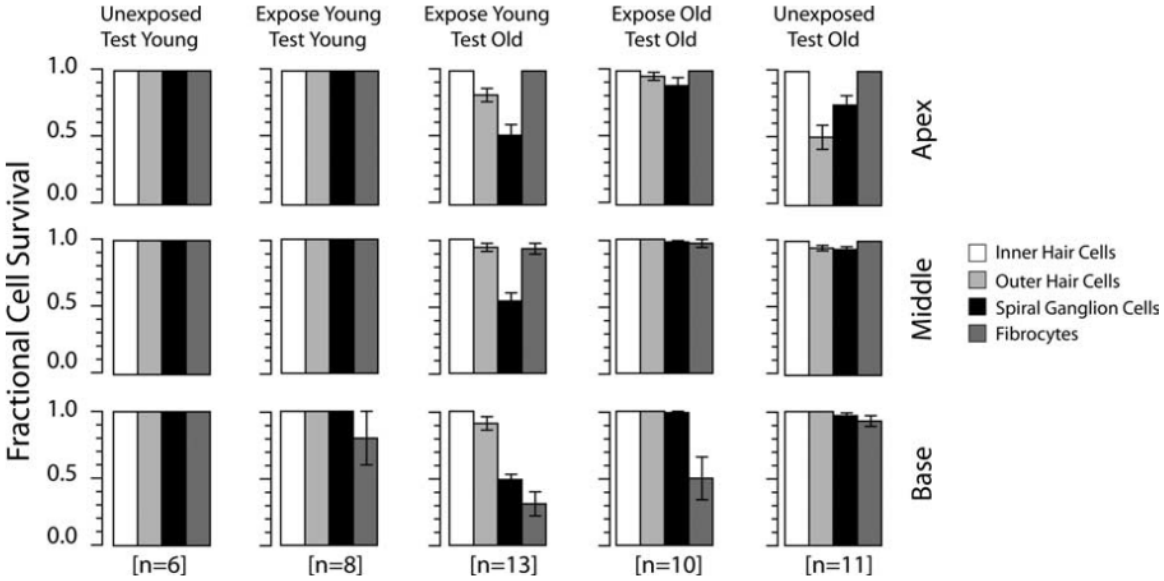


Figure 20 - Effects of noise exposure and normal aging on the survival rate of synapses below the IHC, in mice.
(Source : Kujawa and Liberman, 2006; figure 8, p. 2121)

4.2 Human Studies

In seventeen articles, humans were the experiment subjects: five are cohort studies (5/17; 29.4%), one is a controlled randomized study (1/17; 5.8%); six are time series (6/17; 35.4%) and five are controlled studies (5/17; 29.4%). The studies were grouped together according to the investigation methods used. We find three categories of study: histological studies [n=3, table 5]; studies that use electrophysiological and psychoacoustic measures analogous with those used for the animal models to verify the functioning of fibres showing low spontaneous activity and high triggering thresholds (low-SR fibres for which a vulnerability to noise exposure was clearly demonstrated by the animal studies) [n=7, table 6]; and comparative studies based only on audiometric thresholds [n=8, table 7]. On average, the histological and electrophysiological studies obtain a score of 9.85/14, which places the quality of the corpus analyzed in the category of studies of fair quality (Ali et al., 2008). The audiometric studies obtain a score of 8.4/14, which places them at a lower level than the other types of studies, but they are still placed in the category of studies of fair quality (Ali et al., 2008). The experimental design used to conduct these studies is situated almost totally at level III-2, which provides quite a high level of evidence (Merlin et al., 2009). Appendix 3 presents the analytical grid used in the evaluation of the quality of all the articles retained for analysis, as well as details on the scores obtained.

Table 5 - Summary of human histological studies

HISTOLOGICAL STUDIES				
Number of articles = 3				
Reference	**Type of study**	**Level of evidence**	**Quality assessment (/14 pts.)**	**Sample size (n)**
Bharadwaj, H. M., Masud, S., Mehraei, G., Verhulst, S. and Shinn-Cunningham, B. G. (2015). Individual differences reveal correlates of hidden hearing deficits. *The Journal of Neuroscience*, *35*(5), 2161-2172.[4]	Time series	III-2	9	28
Makary, C. A., Shin, J., Kujawa, S. G., Liberman, M. C. and Merchant, S. N. (2011). Age-related primary cochlear neuronal degeneration in human temporal bones. *Journal of the Association for Research in Otolaryngology*, *12*(6), 711-717.	Time series	III-2	11	100
Viana, L. M., O'Malley, J. T., Burgess, B. J., Jones, D. D., Oliveira, C. A., Santos, F., and Liberman, M. C. (2015). Cochlear neuropathy in human presbycusis: Confocal analysis of hidden hearing loss in post-mortem tissue. *Hearing Research*, *327*, 78-88.	Time series	III-2	9	5
			Mean = 9.7 pts.	

[4] The Bharawaj et al. study (2015) uses both histological and electrophysiological measurements and is therefore found in the two corresponding sections in the table.

Table 6 - Summary of human electrophysiological studies

ELECTROPHYSIOLOGICAL STUDIES				
Number of articles = 7				
Reference	**Type of study**	**Level of evidence**	**Quality assessment (/14 pts.)**	**Sample size (n)**
Bharadwaj, H. M., Masud, S., Mehraei, G., Verhulst, S. and Shinn-Cunningham, B. G. (2015). Individual differences reveal correlates of hidden hearing deficits. *The Journal of Neuroscience*, *35*(5), 2161-2172.	Time series	III-2	9	28
Bramhall, N. F., Konrad-Martin, D., McMillan, G. P. and Griest, S. E. (2017). Auditory Brainstem Response Altered in Humans With Noise Exposure Despite Normal Outer Hair Cell Function. *Ear and Hearing*, *38*(1), e1-e12.	Controlled study	III-2	12	64
Liberman, M. C., Epstein, M. J., Cleveland, S. S., Wang, H. and Maison, S. F. (2016). Toward a differential diagnosis of hidden hearing loss in humans. *PloS One*, *11*(9), e0162726.	Controlled study	III-2	10	34
Mehraei, G., Hickox, A. E., Bharadwaj, H. M., Goldberg, H., Verhulst, S., Liberman, M. C. and Shinn-Cunningham, B. G. (2016). Auditory Brainstem Response Latency in Noise as a Marker of Cochlear Synaptopathy. *The Journal of Neuroscience*, *36*(13), 3755-3764.	Controlled study (open)	III-2	12	23
Prendergast, G., Guest, H., Munro, K. J., Kluk, K., Léger, A., Hall, D. A. and Plack, C. J. (2016). Effects of noise exposure on young adults with normal audiograms I: Electrophysiology. *Hearing Research, 344,* 68–81.	Controlled study	III-2	9	126
Stamper, G. C., and Johnson, T. A. (2015). Auditory function in normal-hearing, noise-exposed human ears. *Ear and Hearing*, *36*(2), 172-184.	Controlled study (open)	III-2	9	30
Stamper, G. C. and Johnson, T. A. (2015). Letter to the Editor: Examination of Potential Sex Influence on Auditory Function in Normal-Hearing, Noise-Exposed Human Ears, *Ear and Hearing, 36*(2), 172-184.	Controlled study (open)	III-2	9	30
			Mean = 10 pts.	

Table 7 - Summary of audiometric studies on humans

AUDIOMETRIC STUDIES				
Number of articles = 8				
Reference	**Type of study**	**Level of evidence**	**Quality assessment (/14 pts.)**	**Sample size (n)**
Albera, R., Lacilla, M., Piumetto, E. and Canale, A. (2010). Noise-induced hearing loss evolution: influence of age and exposure to noise. *European Archives of Oto-Rhino-Laryngology*, *267*(5), 665-671.	Cohort study	III-2	9	30 003
Cruickshanks, K. J., Nondahl, D. M., Tweed, T. S., Wiley, T. L., Klein, B. E., Klein, R. and Nash, S. D. (2010). Education, occupation, noise exposure history and the 10-yr cumulative incidence of hearing impairment in older adults. *Hearing Research*, *264*(1), 3-9.	Time series	III-2	8	28
Gates, G. A., Schmid, P., Kujawa, S. G., Nam, B. H. and D'Agostino, R. (2000). Longitudinal threshold changes in older men with audiometric notches. *Hearing Research*, *141*(1), 220-228.	Cohort study	III-2	10	203
Hederstierna, C. and Rosenhall, U. (2016). Age-related hearing decline in individuals with and without occupational noise exposure. *Noise and Health*, *18*(80), 21.	Cohort study	III-2	9	365
Krishnamurti, S. (2009). Sensorineural hearing loss associated with occupational noise exposure: effects of age-corrections. *International Journal of Environmental Research and Public Health*, *6*(3), 889-899.	Time series	III-2	8	58
Lee, F. S., Matthews, L. J., Dubno, J. R., and Mills, J. H. (2005). Longitudinal study of pure-tone thresholds in older persons. *Ear and Hearing*, *26*(1), 1-11.	Cohort study	III-2	9	188
Rosenhall, U. (2003). The influence of ageing on noise-induced hearing loss. *Noise and Health*, *5*(20), 47.	Cohort study	III-2	6	1485
Xiong, M., Yang, C., Lai, H., and Wang, J. (2014). Impulse noise exposure in early adulthood accelerates age-related hearing loss. *European Archives of Oto-Rhino-Laryngology*, *271*(6), 1351-1354.	Randomized controlled trial	II	8.5	218
			Mean = 8.4 pts.	

4.2.1 Histological Studies

Few histological studies carried out on humans make it possible to establish parallels with the animal studies that have revealed the role of synaptopathy in hearing loss due to noise and aging. Through the literature search, we were able to identify two (Makary et al., 2011; Viana et al., 2015).

The Makary et al. study (2011) quantified the spiral ganglion cells of 100 ears from the Massachusetts Eye and Ear Infirmary's Temporal Bone Registry, which come from human subjects aged 0 to 100 (8 to 12 subjects per decade). The specimens chosen for analysis had no IHC or OHC loss. The findings revealed that, despite the integrity of the hair cells, an annual decline of around 100 spiral ganglion cells between 0 and 100 years was noted, in a linear regression. Figure 21, taken from Makary et al. (2011) illustrates the decline observed among three subjects of different ages (2, 61 and 91 years, respectively). The audiometric thresholds were available for a subset of 33 of the 100 ears analyzed. These data show that hearing thresholds of 250 to 4000 Hz remained within the limits of normal until after the first six decades of life, while we observe, at the same point in time (decade from 51 to 60), the absence of a proportion of 20% of the spiral ganglion cells over the entire cochlear partition (Makary et al., 2011). Three of the specimens examined had been exposed to noise shortly before death. For two of them, there were fewer spiral ganglion cells than what was normally found in their age group, suggesting an increased effect of noise on the degradation that was solely attributable to aging.

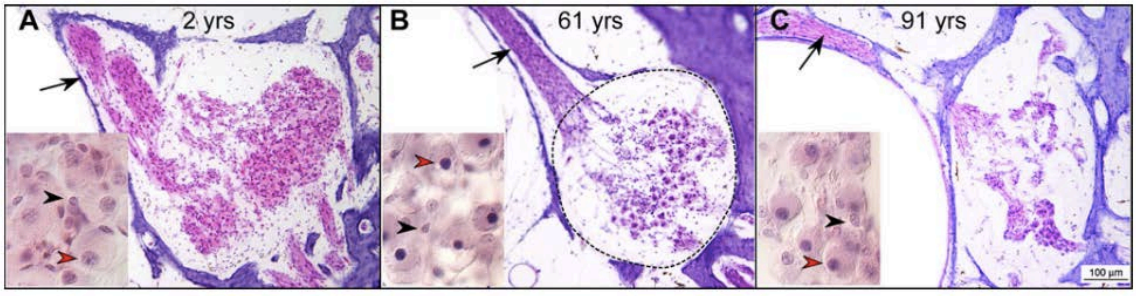


Figure 21 - Photomicrographs illustrating the decrease in numbers of spiral ganglion cells observed with age.
(Source : Makary et al., 2011; figure 2, p. 713)

The preliminary study by Viana et al. (2015), using immunofluorescence, quantitatively examined all of the elements that compose the synapse at the base of the IHC of five ears from the Massachusetts Eye and Ear Infirmary's Temporal Bone Registry, which came from human subjects aged 54 to 89. Despite the integrity of the hair cells in the centre of the cochlear partition, a marked decrease was observed in the presynaptic ribbons from the youngest (between 11.1 and 13.3 synapses per IHC) to the oldest subjects (≤ 7.6 synapses per IHC in the 250 Hz zone and as few as 2 synapses in the 2 kHz zone). Approximately 14 spiral ganglion fibres were observed below each of the IHC at the centre of the cochlear partition of the youngest ear, while there was an almost complete absence of the same fibres in the oldest ear.

The authors also observed that the number of “orphan” synaptic ribbons (i.e., unattached to the postsynaptic cistern) was highest in the basal and apical zones of the cochlea, suggesting that these presynaptic ribbons could have been affected by a synaptopathic process that triggered the degeneration of spiral ganglion fibres (Viana et al., 2015).

4.2.2 Studies Using Electrophysiological and Psychoacoustic Measurements Analogous to Those Used with Animal Models

Given that animal studies dealing with the phenomenon of synaptopathy are relatively recent, there are not yet very many that make it possible to identify valid and reliable indicators of a similar process in humans. The literature search found seven (Bharadwaj et al., 2015; Bramhall et al., 2017; Liberman et al., 2016; Mehraei et al., 2016; Prendergast et al., 2016; Stamper and Johnson, 2015a, 2015b).

These studies identify one or more measures that could specifically target the auditory nerve fibres in humans that (1) show low spontaneous firing rates (low-SR; < 0.5 action potential per second); (2) are not sensitive to low levels of sound stimulation; (3) are stimulated when the amplitude is relatively high; (4) present with a latency period that is longer than fibres with high spontaneous firing rates; (5) can accurately code rapid changes in amplitude (i.e., code the amplitude modulations of an acoustic signal); (6) are particularly vulnerable, according to animal studies, to noise exposure (Furman et al., 2013). The measures that are the most likely to involve this population of neurons are presented in Table 8.

Table 8 - Electrophysiological or psychoacoustic measures with a possible link to the functions of auditory nerve fibres with low spontaneous firing rates (low-SR)

Measure	Hypothesis regarding dysfunction of low-SR fibres	Study[5]	Findings
Electrocochleography Summating potential over action potential ratio (Wave I) SP/AP	The reduction in the total number of fibres leads to a decrease in the amplitude of wave I, while the amplitude of the summating potential (arising from the OHC) remains unchanged, causing an increase in the SP/AP ratio.	Liberman, M. C. et al. (2016)*	SP/AP ratio significantly greater for the group most exposed to noise.
Auditory evoked potential Wave I, silence	The reduction in the total number of fibres leads to a reduction in wave I	Mehraei et al. (2016) Prendergast et al. (2016)* Stamper and Johnson (2015a, 2015b)* Bramhall et al. (2017)*	Divergent results from one study to another.
Auditory evoked potential Wave V, silence	Prior exposure of subjects to noise should explain the observed latency.	Prendergast et al. (2016)*	Wave V latency increases with noise exposure.
Auditory evoked potential Wave V, masked noise	The addition of noise increases wave V latency by disabling the high-SR fibres, for which activity is saturated by the presence of noise and which show a shorter latency than that of low-SR fibres.	Mehraei et al. (2016)	Wave V latency increases with the addition of masked noise. This increase is correlated with the ability to detect interaural time differences in noise
Auditory evoked potential *Envelope following responses (EFR)* *Frequency following responses (FFR)*	The prior exposure of subjects to noise should reduce the ability of the low-SR fibres to code the amplitude modulations of an acoustic signal.	Bharadwaj et al. (2015)* (EFR) Prendergast et al. (2016)* (FFR)	Strong correlation between the EFR response slope and the ability to detect interaural time differences in noise. Weak correlation between the FFR amplitude and the history of noise exposure in men.
Detection threshold of the interaural time difference in noise	The prior exposure of subjects to noise should reduce the ability of low-SR fibres to code the fine temporal differences required to detect interaural differences in time.	Bharadwaj et al. (2015)* Mehraei et al. (2016)	Strong correlation between the ability to detect interaural time differences in noise and the EFR response slope. Significant correlations between the ability to detect interaural time differences in noise and the latency increase of wave V observed in noise.
Detection threshold of the amplitude modulation (AM)	The prior exposure of subjects to noise should reduce the ability of low-SR fibres to code the amplitude modulations of an acoustic signal.	Bharadwaj et al. (2015)*	Significant correlations observed between noise exposure and the increase in AM detection thresholds and the detection of interaural time differences in noise.

[5] The studies identified with an asterisk documented previous noise exposure using a questionnaire or an interview.

Demonstrating the effect of noise exposure that would trigger the process of synaptopathy in humans comes up against two significant problems. The first is the difficulty of accurately examining the noise exposure experienced by the subjects. To date, studies have been conducted using questionnaires and interviews, which depend on the ability of subjects to remember noise exposure over the past year (Stamper and Johnson, 2015a, 2015b) or over their entire lives (Bramhall et al., 2017; Prendergast et al., 2016). At best, one would hope to be able to use these tools to categorize previous exposure (low or high) without being able to quantify it precisely, although recent work by Bramhall et al. (2017) used an approach that could measure noise exposure more precisely. The second problem stems from the considerable natural variation observed among humans (including genetics, a variable that explains almost half of presbycusis variance, according to Yang et al. (2015), compared to laboratory animal populations, for which the genetic make-up is controlled and homogenous).

Despite the limits described in the previous paragraph, studies carried out over the past two years (Table 8) suggest that noise exposure can modify the functioning of the low-SR auditory nerve fibres in human subjects. The measurements that appear most promising in terms of more definitively demonstrating this appear to be correlated in the three studies identified that examined these relationships (Bharadwaj et al., 2015; Mehraei et al., 2016; Prendergast et al., 2016). These measurements are (1) auditory evoked potentials—which measure the wave I amplitude, and the wave latency in the presence of masked noise, EFR or FFR responses; (2) psychoacoustic tests—detection threshold of the amplitude modulation, detection threshold of intra-aural differences in time. The Mehraei et al. study (2016) shows that similar measurements carried out on noise exposed mice that have synaptopathy show the same results as that observed in humans (significant increase in wave V latency when measured in the presence of masked noise). Bramhall et al. (2017) compared the decrease in wave I amplitude in humans (29%) with that observed in animal models (40 to 60%) (Kujawa and Liberman, 2009; Lin et al., 2011).

4.2.3 Comparative Studies Based on Audiometric Thresholds

The most numerous studies that dealt with the influence of noise exposure on the acquisition of presbycusis examined changes in the audiometric thresholds of older people exposed to noise during their active work lives compared to those of older people who had not been as exposed to noise throughout their life, whether from work, through their leisure activities or in their environment. This literature search made it possible to identify eight of these studies (Albera et al., 2010; Cruickshanks et al., 2010; Gates et al., 2000; Hederstierna and Rosenhall, 2016; Krishnamurti, 2009; Lee et al., 2005; Rosenhall, 2003; Xiong et al., 2014). Two theories have been suggested to attempt to explain the effect of noise exposure on hearing loss due to aging. The additive effect theory suggests that the effect of aging is simply added to that of noise in hearing loss. That theory is the foundation of ISO standard 1999:2013 (ISO, 2013). Another theory put forth by Corso in 1980 is based on classical histological observations of the effect of noise exposure on the inner ear, which show the progressive primary destruction of the OHC and the secondary degeneration of the spiral ganglion fibres, to predict that this impairment would not have effects on the acquisition of presbycusis because one part of the cochlea was already destroyed and could not be affected by a second pathological process (Corso, 1980). In that model, presbycusis then affects the areas of the cochlea that were not affected by noise exposure (i.e., frequencies above 6 kHz).

The results of most of the studies identified (n=5) support the Corso (1980) theory (Albera et al., 2010; Cruickshanks et al., 2010; Hederstierna and Rosenhall, 2016; Krishnamurti, 2009; Lee et al., 2005). However, these studies have methodological weaknesses: (1) small sample size (Krishnamurti, 2009, n=68 subjects; Lee et al., 2005, n=97 subjects); (2) the short follow-up time for longitudinal studies (Herderstierna and Rosenhall, 2016, n=5 years; Cruickshanks et al., 2010, n=10 years); (3) inappropriate use of a transversal experimental design to examine the influence of a condition (noise exposure) on the development of hearing loss due to aging (Albera et al., 2010; Krishnamurti, 2009). Those authors did not see a significant influence of prior exposure to noise on the increase in the extent of hearing loss with age, but the experimental designs that were used increase the probabilities of finding this result.

The three other studies came to the opposite conclusion: that noise exposure during the working life accelerates the acquisition of presbycusis (Gates et al., 2000; Rosenhall, 2003; Xiong et al., 2014). With the exception of the Xiong et al. study (2014), which has a major drawback in that it presumes prior exposure to impact noise during the working life without providing evidence of it, the two other studies show a significantly more rapid progression of hearing loss at the frequency of 2 kHz among people exposed to noise during their working lives (Gates et al., 2000; Rosenhall, 2003). Gates et al. (2000) used the presence of a notch at the frequencies of 3, 4 and 6 kHz to prove prior exposure to noise. That approach was strongly contested as not being sufficiently specific to hearing loss due to noise, notably by Cruickshanks et al. (2010), Hederstierna and Rosenhall (2016) and Lee et al. (2005). A recent study by Lie et al. (2016) conducted with 49,774 subjects shows, however, while not being specific, that the presence of a notch at the frequencies of 3 to 6 kHz is more frequent among people exposed to noise in the workplace. The prevalence rate is significantly higher than 10% at the frequency of 4 kHz among men ($p < 0.001$).

4.3 Findings Emerging from the Analysis

The findings from the animal studies come from good quality studies with a high level of evidence. These studies clearly demonstrate that exposure to noise accelerates the process of presbycusis. Some human studies have come to similar conclusions. The findings are based on good quality studies, in which the weight of evidence rests on data from post-mortem analyses and on electrophysiological or psychoacoustic measurements analogous to the animal models. It is not surprising that the findings of poorer quality studies using only audiometric thresholds to evaluate the influence of noise exposure on presbycusis are ambiguous and the weight of evidence is weak. In fact, it has been very clearly demonstrated that cochlear synaptopathy cannot be detected by measuring audiometric thresholds. According to the animal data, synaptopathy caused by noise exposure or by aging can remain undetectable. However, when more sensitive measurements are used, we are able to see that the synaptic damage began several decades before when presbycusis, as traditionally described, would become evident (Schuknecht, 1955). This process is accelerated and magnified by exposure to noise. A number of authors have therefore suggested that the traditional concept of presbycusis, in which this type of hearing loss is due solely to aging (Schuknecht, 1955), should be modified, in that the hearing loss observed with age is the result of the cumulative and synergetic effect of both extrinsic and intrinsic risk factors for hearing impairment, among which is exposure to noise. Figure 22, from Wong and Ryan (2015), illustrates this contemporary view of presbycusis.

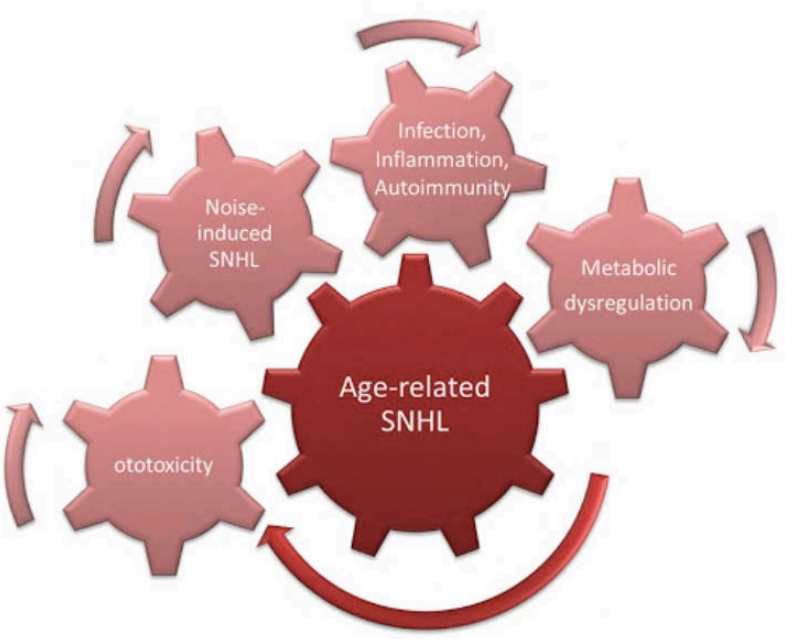


Figure 22 - The cumulative and synergetic effects of factors leading to presbycusis.
(Source : Wong and Ryan, 2015; figure 3, p.9)

5. USE OF CORRECTION FACTORS

The second question to which this literature review must respond is: Can correction factors be used to distinguish occupational hearing loss from presbycusis?

Findings Emerging from the Analysis

The analysis presented in the previous section suggests that a significant portion of the progressive degradation of auditory acuity observed with age could, in fact, be the result of workplace exposure to high levels of noise, or noise exposure prior to employment in a noisy workplace. Figure 20 (last row, third column) from Kujawa and Liberman (2006) illustrates how exposure at the beginning of life among mice (five weeks) takes the form of impairment at the base of the cochlea affecting high frequencies almost two years later (which corresponds to an advanced age in this animal model). Data from Liberman et al. (2016) gathered from a group at risk made up mainly of young music students (average age 25 ± 1.3 years) show hearing threshold impairment at very high frequencies (Figure 23, panel A) similar to the hearing impairment observed in animal models (Fernandez et al., 2015; Kujawa and Liberman, 2006). These recent data call into question the value of correction factors based on the premise that slow degradation of hearing thresholds is uniquely attributable to an intrinsic aging factor, while evidence exists that some of this impairment could be from noise exposure.

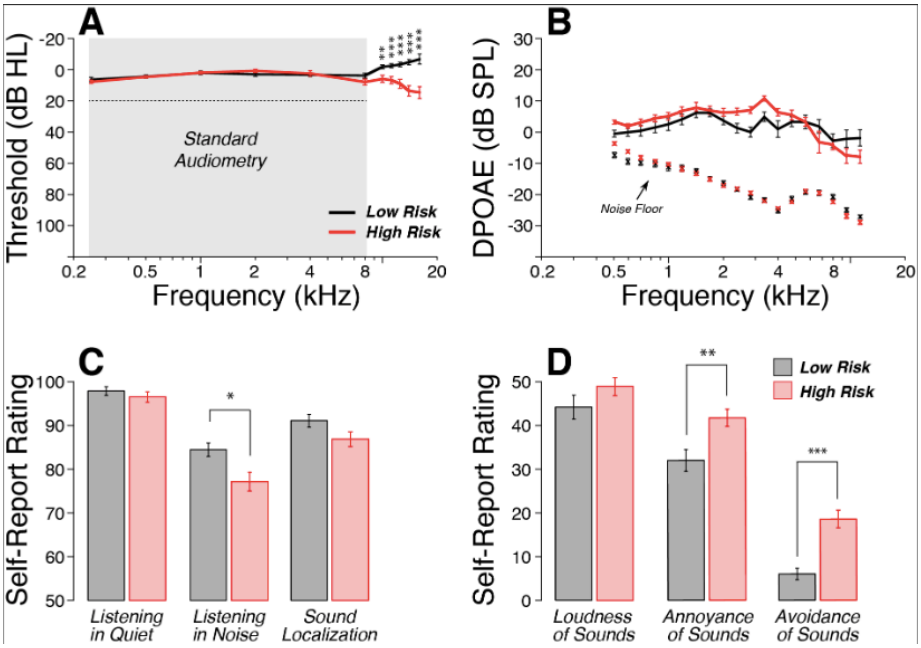


Figure 23 – Audiometric thresholds, autoacoustic emissions and subjective measurements among groups of young adults at low and high risk of hearing impairment due to noise
(source : Liberman et al., 2016; figure 1)

In subsection 5.10 of a document published in 1998 on noise exposure in the workplace, the National Institute for Occupational Safety and Health recommended that age correction not be used because of the great variability that exists among individuals, and that using the median value for presbycusis from a given population could not be applied to an individual (NIOSH, 1998). According to the document, there is a considerable risk of underestimating or overestimating the effect of age, which is impossible to determine with certainty.

6. PROGRESSION OF HEARING LOSS AFTER CESSATION OF NOISE EXPOSURE

The final question asked by the IRSST deals with the progression of hearing loss after excessive noise exposure at work ceases. The intention was to discover whether a worker who has ceased to be exposed to noise in the workplace would continue to experience a decline in hearing independently of aging.

Findings Emerging from the Analysis

The analysis presented in section 3 points to convincing evidence that a moderate to high level of noise exposure (70-85 to 90-100 dB SPL) can trigger the synaptopathy process, at least in animal models (Fernandez et al., 2015; Gannouni et al., 2015; Jensen et al., 2015; Kujawa and Liberman, 2009; Lin et al., 2011; Maison et al., 2013; Mehraei et al., 2016; Song et al., 2016; Wang and Ren, 2012). This process brings about a rapid and permanent destruction of a significant proportion (>40%) of presynaptic ribbons of the IHC, which are in contact with the spiral ganglion fibres that have a low SR (Furman et al., 2013; Jensen et al., 2015; Kujawa and Liberman, 2009; Lin et al., 2011; Song et al., 2016). This destruction does not immediately affect all the hearing thresholds, or the integrity of the OHC (Fernandez et al., 2015; Furman et al., 2013; Jensen et al., 2015; Kujawa and Liberman, 2009; Maison et al., 2013; Mehraei et al., 2016; Song et al., 2016; Wang and Ren, 2012). The destruction of presynaptic ribbons spreads progressively to the IHC situated towards the apex of the cochlea, gradually affecting the lower frequencies (Fernandez et al., 2015; Jensen et al., 2015). The almost immediate destruction of synaptic ribbons and the later process of degeneration of the same structures in other parts in the cochlea are also accompanied by the slow and progressive destruction over time of the spiral ganglion fibres with low-SR activity. This degeneration appears several months, even several years, after noise exposure ceases (Campo et al., 2011; Fernandez et al., 2015; Gannouni et al., 2015; Jensen et al., 2015; Kujawa and Liberman, 2006). When animals that have not been exposed to noise are compared to animals of the same age that were exposed at the beginning of their lives, the gap noted between their hearing thresholds (measured with an electrophysiological equivalent) increases with age (Campo et al., 2011), which indicates that the impairment continues to progress, over and above the effect of aging.

Currently, there are no longitudinal studies of the same nature on humans. However, studies are rapidly progressing and promising measures have been developed over the past two years (Bharadwaj et al., 2015; Bramhall et al., 2017; Mehraei et al., 2016; Prendergast et al., 2016). These measures are (1) auditory evoked potentials: measurement of the amplitude of wave I, measurement of the latency of wave V in the presence of masked noise, EFR or FFR responses; (2) psychoacoustic tests – detection threshold of the amplitude modulation, detection threshold of interaural time differences. The application of these techniques, combined with a rigorous evaluation of noise exposure should make it possible to respond more definitively to this question.

On the molecular level, the animal studies suggest also that cumulative exposure to noise (whether from social or occupational practices) promotes the liberation of free radicals that alter the lipid and protein structures of cells, causing mutations in the mitochondrial DNA. Over a long period, these alterations can progressively elicit the apoptosis of the sensory and nerve cells of the inner ear (Yamasoba et al., 2013). It is therefore conceivable that ending exposure to noise does not guarantee that the underlying physiopathologic processes in the progression of hearing loss (as observed among retired workers) will cease (Gates et al., 2000; Rosenhall, 2003).

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APPENDIX 1 : STRATEGIES USED IN THE DOCUMENT SEARCH ACCORDING TO VARIOUS DATA BASES[6]

PubMed

Acoustic Trauma OR Acquired hearing loss OR Hearing Impairment OR Hearing loss OR Hearing Loss, Mixed Conductive-Sensorineural [MESH] OR Hearing Loss, Sensorineural [Mesh:NoExp] OR Hearing Loss [Mesh:NoExp]

AND

Noise OR noise-exposed OR Noise [MESH] OR Noise, Occupational [MESH]

OR

Hearing Loss, Noise-Induced [MESH] OR Noise Induced Hearing Loss OR Noise/adverse effects [MESH] OR Noise-Induced Hearing Loss

AND

Deafness, Aminoglycoside-Induced [Supplementary Concept] OR Excitotoxicity OR glutamate toxicity OR Glutamates /toxicity [MESH] OR otoprotection OR ototoxicity OR Streptomycin Ototoxicity

OR

age-associated hearing loss OR age-related hearing loss OR aging cochlea OR Cochlear Diseases [MESH] OR Deafness/chemically induced [MESH] OR human temporal bones OR noise-induced cochlear neuropathy OR noise-induced cochlear synaptopathy OR presbycusis OR Presbycusis [MESH]

AND

French OR English

NOT

Child OR Children

TOXLINE

Bruit OR Noise

AND

age-associated hearing loss OR age-related hearing loss OR aging cochlea OR Cochlear Diseases OR human temporal bones OR noise-induced cochlear neuropathy OR noise-induced cochlear synaptopathy OR presbycusis

[6] The strategies used to perform the literature search were designed by Maryse Gagnon, librarian with the Research and Expertise Division of the Institut de recherche Robert-Sauvé en santé et en sécurité du travail.

OSHUPDATE

Acoustic Trauma OR Acquired hearing loss OR Hearing Impairment OR Hearing loss OR noise-exposed OR Noise-Induced

AND

Aminoglycoside-Induced OR Excitotoxicity OR glutamate toxicity OR otoprotection OR ototoxicity OR
age-associated hearing loss OR age-related hearing loss OR aging cochlea OR Cochlear Diseases OR human temporal bones OR noise-induced cochlear neuropathy OR noise-induced cochlear synaptopathy OR presbycusis

ERGONOMICS ABSTRACTS

age-associated hearing loss OR age-related hearing loss OR aging cochlea OR Cochlear Diseases OR human temporal bones OR noise-induced cochlear neuropathy OR noise-induced cochlear synaptopathy OR presbycusis

COCHRANE

age-associated hearing loss OR age-related hearing loss OR aging cochlea OR Cochlear Diseases OR human temporal bones OR noise-induced cochlear neuropathy OR noise-induced cochlear synaptopathy OR presbycusis

CCHST

Acoustic Trauma OR Acquired hearing loss OR Hearing Impairment OR Hearing loss OR noise-exposed OR Noise-Induced

AND

Aminoglycoside-Induced OR Excitotoxicity OR glutamate toxicity OR otoprotection OR ototoxicity OR
age-associated hearing loss OR age-related hearing loss OR aging cochlea OR Cochlear Diseases OR human temporal bones OR noise-induced cochlear neuropathy OR noise-induced cochlear synaptopathy OR presbycusis OR presbyacousie

ISST

Presbycusis

BIOSIS, CURRENT CONTENTS, EMBASE, PASCAL, PROQUEST DISSERTATIONS AND THESES

Option 1:

Acoustic Trauma OR Acquired hearing loss OR Hearing Impairment OR Hearing loss
AND
Bruit OR Noise OR Noise-exposed OR Noise-Induced

AND

age-associated hearing loss OR age-related hearing loss OR aging cochlea OR Cochlear Diseases OR human temporal bones OR noise-induced cochlear neuropathy OR noise-induced cochlear synaptopathy OR presbycusis OR presbyacusis OR presbyacousie

Option 2:

Acoustic Trauma OR Acquired hearing loss OR Hearing Impairment OR Hearing loss
AND
Bruit OR Noise OR Noise-exposed OR Noise-Induced

AND

age-associated hearing loss OR age-related hearing loss OR aging cochlea OR Cochlear Diseases OR human temporal bones OR noise-induced cochlear neuropathy OR noise-induced cochlear synaptopathy OR presbycusis OR presbyacusis OR presbyacousie

AND

Aminoglycoside-Induced OR Excitotoxicity OR glutamate toxicity OR otoprotection OR ototoxicity

GOOGLE SCHOLAR

Noise AND Presbyacusis

APPENDIX 2 : READING NOTES

Appendix 2 presents the detailed analysis notes for the 30 articles retained in this review of the literature. Articles that are irrelevant to the subject and the reviews of the literature were not included. The notes presented are the tools that were used to draft the scientific opinion and do not necessarily provide details of all the study results.

Record 1

Reference	Albera, R., Lacilla, M., Piumetto, E., Canale, A. (2010). Noise-induced hearing loss evolution: influence of age and exposure to noise. *European Archives of Oto-Rhino-Laryngology*, *267*(5), 665–671.
Level of evidence	III-2
Country	Italy
Research question and objectives	Determine the effect of noise and presbycusis on the progression of hearing loss caused by noise and determine whether the changes caused by presbycusis are the same between a noise-exposed group and an unexposed group.
Topic	Effects of noise and presbycusis
Type of study	Cohort study (human)
Participants and groups	568 men with hearing loss caused by noise (group 1, 10–20 years of exposure; group 2, 21–30 years of exposure; group 3, > 30 years of exposure and then stratified by age group (27–35 years, 36–45 years, 56–65 years)).
Intervention	None
Comparator (control group)	No
Measures used	Audiometry from 500 to 8000 Hz over a 2 year period
Analysis of data and statistics	ANOVA; Pearson's chi squared test
Evaluation of the quality of the study and overall evaluation rating	9/14
Findings	Hearing loss due to noise is greater in the first 10 years, but continues to progress over time. Age has an influence on hearing loss in low frequencies among people exposed to noise, although they lose less hearing in high frequencies as they age.
Authors' conclusions	Hearing loss due to noise starts first, while presbycusis affects hearing much later in life. Presbycusis will not progress as rapidly in a group exposed to noise than in a group that has not been exposed (because the cells that have previously been damaged cannot be damaged again).
Evaluator's notes	N/A

Record 2

Reference	Bharadwaj, H. M., Masud, S., Mehraei, G., Verhulst, S., Shinn-Cunningham, B. G. (2015). Individual differences reveal correlates of hidden hearing deficits. *The Journal of Neuroscience*, *35*(5), 2161–2172.
Level of evidence	III-2
Country	United States and Germany
Research question and objectives	Determine the relationships between peripheral function, neural temporal coding and suprathreshold hearing performance.
Topic	Suprathreshold hearing performance et synaptopathy.
Type of study	Time series (human)
Participants and groups	26 subjects + 2 subjects with a “notch”-type hearing loss
Intervention	None
Comparator (control group)	No
Measures used	Audiometry, DPOAE, psychoacoustic and electrophysiological measures
Analysis of data and statistics	Not mentioned
Evaluation of the quality of the study and overall evaluation rating	9/14
Findings	Inter-individual differences in temporal coding among subjects with normal hearing (not related to hearing thresholds or DPOAE). Electrophysiological measures showed that subjects with poor encoding ability found it difficult to detect interaural time differences. They also found it difficult to direct their attention to one message when in the presence of another competing message.
Authors’ conclusions	Synaptopathy affects auditory processing abilities in noisy environments and can be found in people with normal hearing.
Evaluator’s notes	N/A

Record 3

Reference	Bramhall, N. F., Konrad-Martin, D., McMillan, G. P., Griest, S. E. (2017). Auditory Brainstem Response Altered in Humans With Noise Exposure Despite Normal Outer Hair Cell Function. *Ear and Hearing*, *38*(1), e1-e12.
Level of evidence	III-2
Country	United States
Research question and objectives	Determine whether use of ABRs can measure synaptopathy in humans
Topic	Synaptopathy and noise exposure
Type of study	Controlled study (human)
Participants and groups	64 subjects (16 veterans with significant noise exposure; 13 veterans with less noise exposure; 12 non-veterans with a history of firearm use; 23 non-veterans without firearm use)
Intervention	None
Comparator (control group)	Yes, different degrees of exposure to noise
Measures used	Audiometry, DPOAE, BAEP; Questionnaire on the history of noise exposure (LENS-Q)
Analysis of data and statistics	Bayesian regression analysis
Evaluation of the quality of the study and overall evaluation rating	12/14
Findings	Normal audiometry and DPOAE. Groups with the least exposure to noise have the largest wave 1 amplitudes. The group of veterans with little noise exposure and the group of non-veterans without firearm use have a similar wave I amplitude, while the group of veterans with noise exposure and the group of non-veterans with a history of firearm use show a similar reduction in wave I amplitude. No difference for wave III and V.
Authors' conclusions	Wave 1 amplitudes are reduced among subjects exposed to noise. This measure is sensitive for detecting synaptopathy in humans.
Evaluator's notes	N/A

Record 4

Reference	Campo, P., Venet, T., Rumeau, C., Thomas, A., Rieger, B., Cour, C., ..., Parietti-Winkler, C. (2011). Impact of noise or styrene exposure on the kinetics of presbycusis. *Hearing Research*, *280*(1), 122–132.
Level of evidence	III-2
Country	France
Research question and objectives	Determine the effect of 85 dB noise on the presbycusis process
Topic	Noise exposure and presbycusis
Type of study	Controlled study (animal)
Participants and groups	196 rats. Group exposed to noise (n=54), to styrene (n=56) and control group (n=86)
Intervention	Exposure to band noise centred at 8 kHz at 85 dB (6 hours/day, 5 days/week, 4 weeks)
Comparator (control group)	Yes
Measures used	DPOAE, count of IHC/OHC, count of spiral ganglion cells
Analysis of data and statistics	Multifactorial analysis of variance; Bonferroni; Student's t-test
Evaluation of the quality of the study and overall evaluation rating	11/14
Findings	Decrease of DPOAE amplitude with age. Decrease of number of CC and spiral ganglion cells with age. Significant decrease of spiral ganglion cells for the exposed group compared to the control group.
Authors' conclusions	Exposure to noise of even 85 dB could result in an exacerbation of presbycusis.
Evaluator's notes	N/A

Record 5

Reference	Cruickshanks, K. J., Nondahl, D. M., Tweed, T. S., Wiley, T. L., Klein, B. E., Klein, R., ..., Nash, S. D. (2010). Education, occupation, noise exposure history and the 10-yr cumulative incidence of hearing impairment in older adults. *Hearing Research*, *264*(1), 3–9.
Level of evidence	III-2
Country	United States
Research question and objectives	Determine the effect of noise exposure on presbycusis
Topic	Presbycusis and noise exposure
Type of study	Time series (human)
Participants and groups	1925 subjects
Intervention	None
Comparator (control group)	Subjects not exposed to noise
Measures used	Audiometry
Analysis of data and statistics	Chi-squared test; Student's t-test; Mantel Haenszel χ^2 test
Evaluation of the quality of the study and overall evaluation rating	8/14
Findings	Incidence of hearing impairment (37%). Subjects with hearing loss experienced a more rapid progression of the loss. Exposure to noise is not associated with a risk of the progression of hearing impairment (may have caused the impairment, but did not accelerate it in the older population). Men more at risk for hearing impairment than women.
Authors' conclusions	History of noise exposure had no bearing on the progression of the presbycusis
Evaluator's notes	N/A

Record 6

Reference	Fernandez, K. A., Jeffers, P. W., Lall, K., Liberman, M. C., Kujawa, S. G. (2015). Aging after noise exposure: acceleration of cochlear synaptopathy in “recovered” ears. *The Journal of Neuroscience*, *35*(19), 7509–7520.
Level of evidence	III-2
Country	United States
Research question and objectives	Determine the effect of noise exposure on the aging process in mice exposed to various noise levels.
Topic	Hearing loss due to noise and effect on normal aging
Type of study	Controlled study (animal)
Participants and groups	4 groups of an unknown number of mice: group 1 exposed to 100 dB SPL (synaptic exposure); group 2 exposed to 91 dB SPL (non-synaptic exposure); group 2b exposed to 91 dB SPL for 8 hours; group 3 as a control group for age.
Intervention	Exposure to an octave band noise of 8 to 16 kHz, for 2 h.
Comparator (control group)	Yes. Only the effect of age.
Measures used	BAEP, DPOAE, optical microscopy (count of hair cells, spiral ganglion cells and synapses at 5,6, 11,3, 22,6 and 32 kHz).
Analysis of data and statistics	Bonferroni
Evaluation of the quality of the study and overall evaluation rating	11/14
Findings	Increase in the BAEP and DPOAE thresholds 24 hours after exposure, and return to normal after 2 weeks (as much at 100 dB SPL as at 91 dB SPL). 15 to 25% decrease in the number of synapses with age (control). For 91 dB noise for 2 hours, no loss of synapses when measured 2 hr. post-exposure. For 100 dB noise, loss of 35 to 55% of synapses when measured 2 hr. post-exposure (for the 2 high frequencies). No regeneration of synapses up to 88 weeks post-exposure. For the group exposed to 91 dB for 8 hours, there is a loss of synapses (approximately 25%) 24 hr. post-exposure. For mice exposed to 100 dB, the degeneration of synapses ultimately affects the apical areas of the cochlea, which were not directly involved after noise exposure. The number of synapses is lower, even at the apex of the cochlea, than that of the control group. In addition, the loss of synapses continues over time, but more slowly for the group exposed to 100 dB than for the control group. This

	indicates that certain synapses are more vulnerable to noise and age, and once lost after exposure to 100 dB, there are fewer changes due to aging. Loss of spiral ganglion cells with age (approximately 20%). For the group exposed to 100 dB, the decrease in the number of cells began earlier and exceeded the loss of the control group by 25 to 40%. The decrease in the number of internal hair cells was minimal with age and was not amplified by noise exposure noise. For external hair cells, a decrease in number with age, and significant difference at 32 kHz only in relationship with the number of cells in the group exposed to 100 dB. With age, the DPOAE amplitude is relatively stable, but there is a progressive decrease in the amplitude of wave I. For exposure to 100 dB, there is a permanent reduction in wave amplitude I that is more aggravated over time for the control group. The damage progressively affects the OHC.
Authors' conclusions	Not all noise levels producing a temporary threshold shift cause synaptic loss. The degree of synaptopathy is not correlated with the amplitude of threshold shifts. Noise exposure can be permanent and progressive. Exposure to noise exacerbates the synaptic loss that normally takes place with age (the loss begins early and progressively spreads to areas that were not initially affected).
Evaluator's notes	N/A

Record 7

Reference	Furman, A. C., Kujawa, S. G., Liberman, M. C. (2013). Noise-induced cochlear neuropathy is selective for fibres with low spontaneous rates. *Journal of Neurophysiology*, *110*(3), 577–586.
Level of evidence	III-2
Country	United States
Research question and objectives	Determine whether exposure to noise affects fibres with a low level of spontaneous firing rates
Topic	Noise exposure
Type of study	Controlled study (animal)
Participants and groups	9 Guinea pigs exposed
Intervention	Exposure to noise octave band of 4–8 kHz to 106 dB SPL for 2 hours
Comparator (control group)	Yes (n=14)
Measures used	Two weeks post; BAEP, DPOAE, measurement of unitary action potential, count of synapses
Analysis of data and statistics	2-way ANOVA; Kolmogorov-Smirnov
Evaluation of the quality of the study and overall evaluation rating	11/14
Findings	Temporary threshold shift. Partial degeneration of the nerve fibre (permanent drop in wave I). Drop in the number of synapses in exposed ears. Thresholds for fibres with high spontaneous firing rates are the same for two groups. 38% decrease of fibres with low spontaneous firing rates.
Authors' conclusions	Selective synaptopathy of fibres with low spontaneous firing rates.
Evaluator's notes	N/A

Record 8

Reference	Gannouni, N. et al. (2015). Cochlear neuropathy in the rat exposed for a long period to moderate-intensity noises. *Journal of Neuroscience Research*, 93(6): 848–858.
Level of evidence	III-2
Country	France
Research question and objectives	Evaluate whether prolonged exposure or moderate exposure to noise (70 or 85 dB SPL) may cause damage that is observable under electron microscope or optical microscope.
Topic	Synaptopathy
Type of study	Controlled study (animal)
Participants and groups	2 groups, 4 mice exposed to 70 dB SPL, 4 mice exposed to 85 dB SPL, and 4 control mice
Intervention	Exposure to octave band noise 8 to 16 kHz, 6 hr./day for 3 months.
Comparator (control group)	Yes
Measures used	Cell count (OHC, IHC), spiral ganglion neurons, qualitative evaluation
Analysis of data and statistics	Wilcoxon signed-rank test, significance level $p<0.05$
Evaluation of the quality of the study and overall evaluation rating	11/14
Findings	Stable number of CC. Drop in the number of spiral ganglion cells in animals exposed to noise.
Authors' conclusions	Noise levels similar to those permitted by regulations can lead to synaptopathy
Evaluator's notes	N/A

Record 9

Reference	Gates, G. A., Schmid, P., Kujawa, S. G., Nam, B. H., D'Agostino, R. (2000). Longitudinal threshold changes in older men with audiometric notches. *Hearing Research*, *141*(1), 220–228.
Level of evidence	III-2
Country	United States
Research question and objectives	Determine the effect of exposure on the process of presbycusis
Topic	Presbycusis and noise exposure
Type of study	Cohort study (human)
Participants and groups	242 subjects
Intervention	None
Comparator (control group)	Yes (group without a notch)
Measures used	Audiometry
Analysis of data and statistics	Chi-square test; t-test; ANOVA; multivariate analysis of covariance
Evaluation of the quality of the study and overall evaluation rating	10/14
Findings	Progression of presbycusis not the same for the group exposed to noise and the group that was not. Acceleration of hearing loss over time for the areas close to the notch.
Authors' conclusions	Exposure to noise accelerates presbycusis because the hearing loss spreads out into the frequencies adjacent to the hearing loss caused by noise.
Evaluator's notes	N/A

Record 10

Reference	Gleich, O., Semmler, P., Strutz, J. (2016). Behavioral auditory thresholds and loss of ribbon synapses at inner hair cells in aged gerbils. *Experimental Gerontology*, *84*, 61-–70.
Level of evidence	III-2
Country	Germany
Research question and objectives	Determine the link between the number of synapses and thresholds in noise
Topic	Presbycusis and synaptopathy
Type of study	Controlled study (animal)
Participants and groups	6 young Guinea pigs and 8 old ones
Intervention	None
Comparator (control group)	Yes
Measures used	Measurement of thresholds in noise, count of synapses
Analysis of data and statistics	Not mentioned
Evaluation of the quality of the study and overall evaluation rating	11/14
Findings	Decrease in the number of synapses, primarily at the apex of the cochlea in older subjects. Behavioural thresholds not correlated with the number of synapses.
Authors' conclusions	Decrease in the number of synapses with age
Evaluator's notes	N/A

Record 11

Reference	Hederstierna, C., Rosenhall, U. (2016). Age-related hearing decline in individuals with and without occupational noise exposure. *Noise and Health*, *18*(80), 21.
Level of evidence	III-2
Country	Sweden
Research question and objectives	Describe the evolution of presbycusis and determine the link between decline in hearing and the history of noise exposure
Topic	Presbycusis and noise exposure
Type of study	Cohort study (human)
Participants and groups	365 subjects
Intervention	None
Comparator (control group)	Yes
Measures used	Audiometry 250 to 8000 Hz
Analysis of data and statistics	Nonparametric tests: Kruskal–Wallis and Mann–Whitney *U*
Evaluation of the quality of the study and overall evaluation rating	9/14
Findings	No difference in hearing degradation between the group exposed to noise and the group that was not exposed to noise.
Authors' conclusions	The presbycusis model does not differ between the two groups.
Evaluator's notes	N/A

Record 12

Reference	Jensen, J. B., Lysaght, A. C., Liberman, M. C., Qvortrup, K., Stankovic, K. M. (2015). Immediate and delayed cochlear neuropathy after noise exposure in pubescent mice. *PloS One*, *10*(5), e0125160.
Level of evidence	III-2
Country	United States
Research question and objectives	Determine the psychological and histological effects of exposure to differing intensities of noise.
Topic	Effects of noise
Type of study	Controlled study (animal)
Participants and groups	142 animals. Group 1 exposed to 94, group 2 to 97 and group 3 to 100 dB SPL
Intervention	Exposure to octave band noise of 8 to 16 kHz, 94 or 97 or 100 dB SPL for 2 hr.
Comparator (control group)	Yes
Measures used	BAEP, DPOAE, optical microscopy (count of sensory cells, spiral ganglion cells, synapses). Measurements of thresholds repeated at 6 hours, 2 and 4 weeks, 10 and 16 months post-exposure.
Analysis of data and statistics	Two-way ANOVA; post hoc two-sample *t*-test with pooled-variance; one-way ANOVA and post hoc Dunnett's multiple comparisons test
Evaluation of the quality of the study and overall evaluation rating	11/14
Findings	Temporary threshold shift for the 3 groups, but the group at 100 dB experienced a permanent increase of amplitude of wave I. No change in the DPOAE. For group 94 dB, no decrease in the number of synapses. For group 97 dB, a significant decrease (55%) compared to the control group. No regeneration. Reduction in the number of synapses with age also. No loss of CC. Loss of peripheral axons in the cochlear nerve for the group exposed to noise.
Authors' conclusions	The noise levels that create a temporary elevation of thresholds, without loss of CC, can destroy almost 40 to 50% of synapses between the nerve and the IHC. The effects of noise may appear years later (instantaneous loss of synapses at the base of the cochlea, extending afterward toward the apex. At 16 months, there is a significant difference in the number of synapses at the apex of the cochlea, compared to the control group. Therefore, noise exposure accelerates the process of presbycusis when synaptopathy moves from the high frequencies toward the low frequencies.
Evaluator's notes	N/A

Record 13

Reference	Krishnamurti, S. (2009). Sensorineural hearing loss associated with occupational noise exposure: effects of age-corrections. *International Journal of Environmental Research and Public Health*, *6*(3), 889–899.
Level of evidence	III-2
Country	United States
Research question and objectives	Determine the effect of using correction factors to distinguish presbycusis from noise exposure.
Topic	Presbycusis and noise exposure
Type of study	Time series (human)
Participants and groups	68 subjects (retrospective analysis of files), in 4 age groups (50–59 years, 60–69 years, 70–79 years, 80–89 years)
Intervention	None
Comparator (control group)	No
Measures used	Audiometry 500 to 8000 Hz
Analysis of data and statistics	Multiple variance analysis
Evaluation of the quality of the study and overall evaluation rating	8/14
Findings	Only 50% of subjects had a notch.
Authors' conclusions	Interaction between age and noise exposure that differs according to age groups. Noise exposure does not magnify presbycusis (because the portion attributable to noise when there is a hearing impairment decreases over time) → contrary to what has been found in the animal studies. The effects of noise on hearing decelerate with age and the effects of presbycusis accelerate with age
Evaluator's notes	N/A

Record 14

Reference	Kujawa, S. G., Liberman, M.C. (2006). Acceleration of age-related hearing loss by early noise exposure: evidence of a misspent youth. *J Neurosci* 26(7): 2115–2123.
Level of evidence	III-2
Country	United States
Research question and objectives	Determine the effect of noise exposure on the aging process of mice identically exposed at different ages
Topic	Hearing loss due to noise and effect on normal aging
Type of study	Controlled study (animal)
Participants and groups	354 rats exposed at different times in life and tested at different times post-exposure
Intervention	Exposure to octave band noise 8 to 16 kHz, 100 dB SPL for 2 h. Exposure at different ages: 4, 6, 8, 16, 32, 64, 96 and 124 weeks of life.
Comparator (control group)	Yes
Measures used	BAEP, DPOAE, optical microscopy (count of sensory cells, spiral ganglion cells, stria vascularis, spiral ligament and spiral limbus). Measurements of thresholds repeated at 2, 16, 32, 64 and 96 weeks post-exposure.
Analysis of data and statistics	Not mentioned
Evaluation of the quality of the study and overall evaluation rating	10/14
Findings	Deterioration in the neuronal response in the group of mice exposed to noise. Mice exposed to noise show an increase in presbycusis as they age.
Authors' conclusions	Noise exposure at a young age makes the ear more susceptible to acceleration of the presbycusis with age.
Evaluator's notes	N/A

Record 15

Reference	Kujawa, S. G., Liberman, M. C. (2009). Adding insult to injury: cochlear nerve degeneration after “temporary” noise-induced hearing loss. *The Journal of Neuroscience*, *29*(45), 14077–14085.
Level of evidence	III-2
Country	United States
Research question and objectives	Determine the effect of a temporary threshold shift (noise exposure) on the nerve endings.
Topic	Noise exposure
Type of study	Controlled study (animal)
Participants and groups	Exposed group and control group
Intervention	Exposure to octave band noise (8–16 kHz) to 100 dB SPL for two hours, at 16 weeks of life.
Comparator (control group)	Yes (n=11)
Measures used	BAEP, DPOAE and measure of composite action potential; count of synapses and spiral ganglion cells and count of IHC/OHC.
Analysis of data and statistics	Not mentioned
Evaluation of the quality of the study and overall evaluation rating	10/14
Findings	Decrease in neural response (BAEP) while the DPOAE return to normal. No loss of IHC/OHC. Loss of synapses. Decrease in the density of auditory fibres.
Authors’ conclusions	Despite a reversible threshold shift and no damage to the CC, progressive damage of the synapses and auditory fibres.
Evaluator’s notes	N/A

Record 16

Reference	Lee, F. S., Matthews, L. J., Dubno, J. R., Mills, J. H. (2005). Longitudinal study of pure-tone thresholds in older persons. *Ear and Hearing*, *26*(1), 1–11.
Level of evidence	III-2
Country	United States
Research question and objectives	Identify the process of presbycusis on hearing loss and relate it to age, gender and noise exposure.
Topic	Presbycusis and noise exposure
Type of study	Cohort study (human)
Participants and groups	188 adults with presbycusis
Intervention	None
Comparator (control group)	No
Measures used	Tonal audiometry
Analysis of data and statistics	Not mentioned
Evaluation of the quality of the study and overall evaluation rating	9/14
Findings	Subjects with greater hearing loss in middle frequencies lose hearing in the low frequencies more rapidly.
Authors' conclusions	No difference in hearing deterioration for those exposed and those not exposed to noise → contrary to Gates. Older people lose their hearing more rapidly than young people.
Evaluator's notes	N/A

Record 17

Reference	Liberman, M. C., Epstein, M. J., Cleveland, S. S., Wang, H., Maison, S. F. (2016). Toward a differential diagnosis of hidden hearing loss in humans. *PloS One*, *11*(9), e0162726.
Level of evidence	III-2
Country	United States
Research question and objectives	Determine whether synaptopathy exists in humans and what tools can measure it.
Topic	Synaptopathy and exposure to noise
Type of study	Controlled study (human)
Participants and groups	34 subjects divided into two groups: Low and high risk of synaptopathy
Intervention	None
Comparator (control group)	Yes (low risk group)
Measures used	Audiometry + high frequency audiometry, vocal in noise, DPOAE, electrocochleography (BAEP with ear canal electrodes)
Analysis of data and statistics	Two-tailed heteroscedastic *t*-tests; Two-way ANOVA.
Evaluation of the quality of the study and overall evaluation rating	10/14
Findings	Normal audiometry. High frequency audiometry thresholds not as good for high-risk group. Normal DPOAE for two groups. High risk group had a lower score for vocal in noise and report intolerance to sounds. Significant difference in the summating potential amplitude between the two groups. SP/AP correlated with difficulties in noise.
Authors' conclusions	Loss of high frequency threshold could indicate the presence of synaptopathy
Evaluator's notes	N/A

Record 18

Reference	Lin, H. W., Furman, A. C., Kujawa, S. G., Liberman, M. C. (2011). Primary neural degeneration in the Guinea pig cochlea after reversible noise-induced threshold shift. *Journal of the Association for Research in Otolaryngology*, *12*(5), 605–616.
Level of evidence	III-2
Country	United States
Research question and objectives	Determine the effect of noise
Topic	Exposure to noise and synaptopathy
Type of study	Controlled study (animal)
Participants and groups	Guinea pig
Intervention	Exposure to octave band noise (4–8 kHz) for 2 hours at 106 or 109 dB SPL (several analyses post-exposure from 24 h to 6 weeks, and 2 years later).
Comparator (control group)	Yes
Measures used	BAEP, DPOAE, count of CC and spiral ganglion cells.
Analysis of data and statistics	Two-way ANOVA
Evaluation of the quality of the study and overall evaluation rating	11/14
Findings	Drop in the number of synapses after one episode of noise exposure, as was the case in rats.
Authors' conclusions	Irreversible neuronal damage caused by noise exposure.
Evaluator's notes	N/A

Record 19

Reference	Maison, S.F., Usubuchi, H., Liberman, M.C. (2013). Efferent feedback minimizes cochlear neuropathy from moderate noise exposure. *J. Neurosci.* 33, 5542–5552.
Level of evidence	III-2
Country	United States
Research question and objectives	Determine the link between exposure to noise of moderate intensity and synaptopathy.
Topic	Synaptopathy and exposure to noise
Type of study	Controlled study (animal)
Participants and groups	Control and exposed group (27 subjects)
Intervention	Exposure to octave band noise of 8 to16 kHz at 84 dP SPL for 1 week
Comparator (control group)	Yes
Measures used	BAEP; OAE, count of spiral ganglion cells; measurement of degree of deafferentation.
Analysis of data and statistics	Not mentioned
Evaluation of the quality of the study and overall evaluation rating	11/14
Findings	Mice with intact afferent systems with hearing loss not caused by exposure to noise. In the case of animals with deafferentation, loss of 40% of synapses and decrease of the ABR wave I amplitude.
Authors' conclusions	Synaptopathy possible even in day-to-day acoustic environments.
Evaluator's notes	N/A

Record 20

Reference	Makary, C. A., Shin, J., Kujawa, S. G., Liberman, M. C., Merchant, S. N. (2011). Age-related primary cochlear neuronal degeneration in human temporal bones. *Journal of the Association for Research in Otolaryngology*, *12*(6), 711–717.
Level of evidence	III-2
Country	United States
Research question and objectives	Determine the number of spiral ganglion cells in humans in terms of presbycusis.
Topic	Presbycusis and exposure to noise
Type of study	Time series (human)
Participants and groups	100 ears from 100 cadavers (from 0 to100 years) → 3 subjects had been exposed to noise
Intervention	None
Comparator (control group)	None
Measures used	Count of spiral ganglion cells
Analysis of data and statistics	Linear regression
Evaluation of the quality of the study and overall evaluation rating	11/14
Findings	Decrease in the number of spiral ganglion cells with age, even with no loss of hair cells. Two of the three subjects exposed to noise had fewer spiral ganglion cells than others in their age group.
Authors' conclusions	The numbers of spiral ganglion cells decrease with age, which may explain comprehension difficulties in noise observed in old people.
Evaluator's notes	N/A

Record 21

Reference	Mehraei, G., Hickox, A. E., Bharadwaj, H. M., Goldberg, H., Verhulst, S., Liberman, M. C., Shinn-Cunningham, B. G. (2016). Auditory Brainstem Response Latency in Noise as a Marker of Cochlear Synaptopathy. *The Journal of Neuroscience*, *36*(13), 3755–3764.
Level of evidence	III-2
Country	United States
Research question and objectives	Determine whether the effect of noise on wave V can predict synaptopathy.
Topic	Synaptopathy
Type of study	Controlled study (human et animal)
Participants and groups	23 adults with normal hearing; 63 mice
Intervention	Mice exposed to octave band noise of 8 to16 kHz for 2 hours at100 or 94 dB SPL
Comparator (control group)	Yes
Measures used	BAEP; count of spiral ganglion cells.
Analysis of data and statistics	Correlation analysis, statistical inference using mixed-effects models et post hoc analyses.
Evaluation of the quality of the study and overall evaluation rating	12/14
Findings	Among mice, decrease in the number of synapses when exposed to noise + drop in wave I amplitude + wave V latency shift when the masked noise level is increased. Among humans, inter-individual differences in the wave V latency shift in the presence of masking noise. Subjects with an increase in wave V also present with difficulties in temporal coding.
Authors' conclusions	Measurements of the effects of noise on wave V latency can be used to detect synaptopathy in humans.
Evaluator's notes	N/A

Record 22

Reference	Prendergast, G., Guest, H., Munro, K. J., Kluk, K., Léger, A., Hall, D. A., ..., Plack, C. J. (2016). Effects of noise exposure on young adults with normal audiograms I: Electrophysiology. *Hearing Research, 344*, 68–81.
Level of evidence	III-2
Country	United Kingdom and the United States
Research question and objectives	Determine whether BAEP and FFR can detect synaptopathy in humans.
Topic	Noise exposure and synaptopathy
Type of study	Controlled study (human)
Participants and groups	126 participants with different levels of noise exposure.
Intervention	None.
Comparator (control group)	Yes (subjects less exposed to noise)
Measures used	Pure tone audiometry + high-frequency audiometry, TEOAE, ABR, FFR.
Analysis of data and statistics	Pearson
Evaluation of the quality of the study and overall evaluation rating	9/14
Findings	No relationship between TEOAE and noise exposure. Normal audiometry. No loss in amplitude according to noise exposure. FFR decreases according to exposure to noise for men.
Authors' conclusions	No evidence that a decrease of wave I of the ABR is correlated with noise exposure in humans (no synaptopathy if the audiogram is normal? synaptopathy is already present and does not change according to noise exposure? Or the tools are not sensitive enough?). No evidence of synaptopathy in humans with normal hearing thresholds. Synaptopathy cannot occur in humans when there is no threshold shift.
Evaluator's notes	N/A

Record 23

Reference	Rosenhall, U. (2003). The influence of ageing on noise-induced hearing loss. *Noise and Health*, *5*(20), 47.
Level of evidence	III-2
Country	Sweden
Research question and objectives	Establish a link between presbycusis et noise exposure.
Topic	Presbycusis and noise exposure
Type of study	Cohort study (human)
Participants and groups	1485 subjects (4 cohorts)
Intervention	None
Comparator (control group)	Yes
Measures used	Audiometry
Analysis of data and statistics	Not mentioned
Evaluation of the quality of the study and overall evaluation rating	6/14
Findings	Significant differences in the thresholds of those exposed to noise and those not exposed (in the area of the notch and at 1 to 2 kHz). Subjects report 2 times more tinnitus in the group exposed to noise.
Authors' conclusions	Noise exposure before presbycusis slows presbycusis in the areas of hearing loss related to noise but accelerates the presbycusis in adjacent areas.
Evaluator's notes	N/A

Record 24

Reference	Sergeyenko, Y., Lall, K., Liberman, M. C., Kujawa, S. G. (2013). Age-related cochlear synaptopathy: an early-onset contributor to auditory functional decline. *The Journal of Neuroscience*, *33*(34), 13686–13694.
Level of evidence	III-2
Country	United States
Research question and objectives	Determine the effect of aging on cochlear synapses in mice not exposed to noise.
Topic	Synaptopathy and presbycusis.
Type of study	Time series (animal)
Participants and groups	Mice from 4 to 144 weeks of life, with non-invasive measurements taken at 4, 16, 32, 64, 80, 96, 128, 144 weeks.
Intervention	None (aging)
Comparator (control group)	No
Measures used	BAEP, DPOAE, optical microscopy (count of OHC/IHC, spiral ganglion cells, synaptic ribbons)
Analysis of data and statistics	Not mentioned
Evaluation of the quality of the study and overall evaluation rating	10/14
Findings	Slow and gradual rise in thresholds (BAEP + DPOAE) of medium and high frequencies until 96 weeks of life. Afterward, the rise is more rapid and affects all the frequencies. Loss appears more rapidly in the BAEP than the DPOAE. No loss of IHC. Loss of OHC as of 80 weeks of life (from the apex toward the base). Progressive loss of cells of the spiral ganglion over time (up to 40% in the older mice). Gradual decrease in the number of synapses with the IHC with age (preservation of synapses with OHC).
Authors' conclusions	Synaptic ribbons provide an estimate of the number of auditory fibres. Wave I enables the integrity of the auditory fibres of the auditory nerve to be measured → correlation between synaptopathy and BAEP in humans with normal hearing. Loss of cells of the spiral ganglion before the CC, at a similar rate as found in humans (see Makary et al., 2011). However, the count of cells of the spiral ganglion underestimates the synaptopathy.
Evaluator's notes	N/A

Record 25

Reference	Song, Q., Shen, P., Li, X., Shi, L., Liu, L., Wang, J., ..., Wang, J. (2016). Coding deficits in hidden hearing loss induced by noise: the nature and impacts. *Scientific Reports*, *6*.
Level of evidence	III-2
Country	China and Canada
Research question and objectives	Determine the effect of exposure noise on the auditory fibre.
Topic	Noise exposure
Type of study	Controlled study (animal)
Participants and groups	64 hamsters (control group, group 1 evaluated 1 day post, group 2 evaluated 1 week post and group 3 evaluated 1 month post)
Intervention	Exposure to a noise of 105 dB SPL over 2 hours
Comparator (control group)	Yes
Measures used	BAEP, DPOAE, measurement of the composite action potential, optical microscopy (count of synapses)
Analysis of data and statistics	One-way ANOVA; post-hoc tests
Evaluation of the quality of the study and overall evaluation rating	11/14
Findings	Decrease in the number of synapses and the PAC amplitude.
Authors' conclusions	Repair of synapses after they are damaged. Decrease in the number of synapses that enervate fibres with low spontaneous discharge rates.
Evaluator's notes	N/A

Record 26

Reference	Stamper, G. C., Johnson, T. A. (2015a). Auditory function in normal-hearing, noise-exposed human ears. *Ear and Hearing*, *36*(2), 172.
Level of evidence	III-2
Country	United States
Research question and objectives	Characterize the suprathreshold and neural functions among subjects with differing degrees of noise exposure
Topic	Noise exposure
Type of study	Open study (human)
Participants and groups	30 subjects with normal hearing.
Intervention	None
Comparator (control group)	Yes (different NEQ scores)
Measures used	Audiometry, DPOAE, BAEP
Analysis of data and statistics	Linear regression analyses
Evaluation of the quality of the study and overall evaluation rating	9/14
Findings	NEQ value between 67 and 83 dB. Normal DPOAE and no link between NEQ value and DPOAE. Wave I amplitude lessened according to the NEQ. Wave V amplitude does not change.
Authors' conclusions	Wave I amplitude smaller among subjects with a greater exposure to noise (at high intensity of stimulation). The results support the data from animal studies on synaptopathy.
Evaluator's notes	N/A

Record 27

Reference	*Stamper, G. C., Johnson, T. A. (2015b). Letter to the Editor: Examination of Potential Sex Influence on Auditory Function in Normal-Hearing, Noise-Exposed Human Ears, *Ear and Hearing*, *36*(2), 172–184.
Level of evidence	
Country	
Research question and objectives	
Topic	
Type of study	
Participants and groups	
Intervention	
Comparator (control group)	
Measures used	
Analysis of data and statistics	Linear regression analyses (male group and female group)
Evaluation of the quality of the study and overall evaluation rating	
Findings	
Authors' conclusions	Reduction of wave I amplitude only in women exposed to noise.
Evaluator's notes	*Parameters of the study described previously by Stamper, G. C. and Johnson, T. A. (2015a). Auditory function in normal-hearing, noise-exposed human ears. *Ear and Hearing*, *36*(2), 172 (*see Record 26). Secondary analyses conducted after publication of the original article.

Record 28

Reference	Viana, L. M., O'Malley, J. T., Burgess, B. J., Jones, D. D., Oliveira, C. A., Santos, F., ..., Liberman, M. C. (2015). Cochlear neuropathy in human presbycusis: Confocal analysis of hidden hearing loss in post-mortem tissue. *Hearing Research*, *327*, 78–88.
Level of evidence	III-2
Country	United States and Brazil
Research question and objectives	Determine the presence of synaptopathy among human subjects.
Topic	Presbycusis and synaptopathy
Type of study	Time series (human)
Participants and groups	5
Intervention	None
Comparator (control group)	No
Measures used	Count of synapses, CC, neurons.
Analysis of data and statistics	Quantitative analysis without statistical analysis.
Evaluation of the quality of the study and overall evaluation rating	9/14
Findings	Loss of spiral ganglion cells through aging, while the CC population remains almost normal.
Authors' conclusions	The loss of spiral ganglion cells could indicate a process of synaptopathy underlying the presbycusis, which could explain the difficulties in understanding in noise, with an almost normal audiogram.
Evaluator's notes	N/A

Record 29

Reference	Wang, Y., Ren, C. (2012). Effects of repeated “benign” noise exposures in young CBA mice: shedding light on age-related hearing loss. *Journal of the Association for Research in Otolaryngology*, *13*(4), 505–515.
Level of evidence	II
Country	United States
Research question and objectives	Determine the histological and psychological effects of repeated temporary auditory threshold shifts.
Topic	Hearing loss due to noise.
Type of study	Randomized controlled trial (animal)
Participants and groups	3 randomized groups; 1x, 2x et 3x noise exposure of 100 dB SPL
Intervention	Exposure (1x; 2x; 3x) to an octave band noise centred at 12 kHz, for 2 h, at 100 dB SPL, at 4, 6 and 8 weeks of life.
Comparator (control group)	Yes.
Measures used	BAEP, DPOAE, optical microscopy (count of hair cells and synapses) 24 h and 2 weeks post-exposure
Analysis of data and statistics	Two-way ANOVA; post- hoc pairwise comparison
Evaluation of the quality of the study and overall evaluation rating	12/14
Findings	Temporary threshold shift of BAEP post-exposure, but the animals exposed to three doses experienced a permanent threshold shift. Reduction of temporary post-exposure DPOAE for groups 1 and 2. For group 3, permanent reduction of DPOAE at 23 kHz. Similar decrease in synapses for group 1 and 2. Significant decrease in synapses for group 3 compared to all the other groups. No loss of internal or external hair cells. No loss of spiral ganglion cells, but loss of type IV fibrocytes in all the animals exposed to noise.
Authors’ conclusions	Repeated temporary threshold shifts lead to hearing loss similar to presbycusis. Different structures may be affected when moving from a temporary shift to a permanent hearing loss. Increase in thresholds (BAEP) corresponds with a loss of synapses. An accumulation of cochlear and neuronal damage with recurrent exposure to noise may be a contributing factor to presbycusis. No protective effect from a prior exposure to noise.
Evaluator’s notes	N/A

Record 30

Reference	Xiong, M., Yang, C., Lai, H., Wang, J. (2014). Impulse noise exposure in early adulthood accelerates age-related hearing loss. *European Archives of Oto-Rhino-Laryngology*, *271*(6), 1351–1354.
Level of evidence	II
Country	China
Research question and objectives	Determine the effect of impact noise on the progression of presbycusis.
Topic	Presbycusis and exposure to noise.
Type of study	Randomized controlled trial (human)
Participants and groups	109 subjects in the control group; 109 army veterans, exposed between 20 to 25 years old to battle noise, then not exposed to noise after leaving the army (with normal hearing).
Intervention	None
Comparator (control group)	Yes (never exposed to noise)
Measures used	Tonal audiometry (125 to 8000 Hz)
Analysis of data and statistics	Test *t* (Student)
Evaluation of the quality of the study and overall evaluation rating	8.5/14
Findings	No differences in the means of pure sounds between the two groups. Significant difference in the means of high frequency sounds between the two groups.
Authors' conclusions	Presbycusis accelerated by exposure to noise when young.
Evaluator's notes	N/A

APPENDIX 3 : ASSESSMENT PROCESS FOR THE QUALITY OF ARTICLES

The process to assess the quality of articles is based on the analysis table in Ali et al., 2008.

	Randomization (/2)	**Similar groups (/2)**	**Inclusion and exclusion criteria (/2)**	**Results measured in a standard and valid way (/2)**	**Analysis strategies adequately described (/2)**	**Subjects excluded described completely (/2)**	**Control of demographic characteristics and confounding variables (/2)**	**Total score (/14)**
Albera, R., Lacilla, M., Piumetto, E., Canale, A. (2010). Noise-induced hearing loss evolution: influence of age and exposure to noise. *European Archives of Oto-Rhino-Laryngology*, *267*(5), 665-671	0	1	2	2	2	1	1	**9**
Bharadwaj, H. M., Masud, S., Mehraei, G., Verhulst, S., Shinn-Cunningham, B. G. (2015). Individual differences reveal correlates of hidden hearing deficits. *The Journal of Neuroscience*, *35*(5), 2161–2172.	0	1	1	2	2	1	2	**9**
Bramhall, N. F., Konrad-Martin, D., McMillan, G. P., Griest, S. E. (2017). Auditory Brainstem Response Altered in Humans With Noise Exposure Despite Normal Outer Hair Cell Function. *Ear and Hearing*, *38*(1), e1-e12.	0	2	2	2	2	2	2	**12**

	Randomization (/2)	**Similar groups (/2)**	**Inclusion and exclusion criteria (/2)**	**Results measured in a standard and valid way (/2)**	**Analysis strategies adequately described (/2)**	**Subjects excluded described completely (/2)**	**Control of demographic characteristics and confounding variables (/2)**	**Total score (/14)**
Campo, P., Venet, T., Rumeau, C., Thomas, A., Rieger, B., Cour, C., ..., Parietti-Winkler, C. (2011). Impact of noise or styrene exposure on the kinetics of presbycusis. *Hearing Research*, *280*(1), 122–132.	0	2	1	2	2	2	2	**11**
Cruickshanks, K. J., Nondahl, D. M., Tweed, T. S., Wiley, T. L., Klein, B. E., Klein, R., ..., Nash, S. D. (2010). Education, occupation, noise exposure history and the 10-yr cumulative incidence of hearing impairment in older adults. *Hearing Research*, *264*(1), 3–9.	0	1	1	2	2	1	1	**8**
Fernandez, K. A., Jeffers, P. W., Lall, K., Liberman, M. C., Kujawa, S. G. (2015). Aging after noise exposure: aOHCleration of cochlear synaptopathy in “recovered” ears. *The Journal of Neuroscience*, *35*(19), 7509–7520.	0	2	1	2	2	2	2	**11**
Furman, A. C., Kujawa, S. G., Liberman, M. C. (2013). Noise-induced cochlear neuropathy is selective for fibres with low spontaneous rates. *Journal of Neurophysiology*, *110*(3), 577–586.	0	2	1	2	2	2	2	**11**
Gannouni, N. et al. (2015). Cochlear neuropathy in the rat exposed for a long period to moderate-intensity noises. *J Neurosci Res*, 93(6): 848–858.	0	2	1	2	2	2	2	**11**

	Randomization (/2)	Similar groups (/2)	Inclusion and exclusion criteria (/2)	Results measured in a standard and valid way (/2)	Analysis strategies adequately described (/2)	Subjects excluded described completely (/2)	Control of demographic characteristics and confounding variables (/2)	Total score (/14)
Gates, G. A., Schmid, P., Kujawa, S. G., Nam, B. H., D'Agostino, R. (2000). Longitudinal threshold changes in older men with audiometric notches. *Hearing Research*, *141*(1), 220–228.	0	1	2	2	2	2	1	**10**
Gleich, O., Semmler, P., Strutz, J. (2016). Behavioral auditory thresholds and loss of ribbon synapses at inner hair cells in aged gerbils. *Experimental Gerontology*, *84*, 61–70.	0	2	1	2	2	2	2	**11**
Hederstierna, C., Rosenhall, U. (2016). Age-related hearing decline in individuals with and without occupational noise exposure. *Noise and Health*, *18*(80), 21.	0	1	2	2	2	1	1	**9**
Jensen, J. B., Lysaght, A. C., Liberman, M. C., Qvortrup, K., Stankovic, K. M. (2015). Immediate and delayed cochlear neuropathy after noise exposure in pubescent mice. *PloS One*, *10*(5), e0125160.	0	2	1	2	2	2	2	**11**
Krishnamurti, S. (2009). Sensorineural hearing loss associated with occupational noise exposure: effects of age-corrections. *International Journal of Environmental Research and Public Health*, *6*(3), 889–899.	0	1	2	2	2	1	0	**8**

	Randomization (/2)	Similar groups (/2)	Inclusion and exclusion criteria (/2)	Results measured in a standard and valid way (/2)	Analysis strategies adequately described (/2)	Subjects excluded described completely (/2)	Control of demographic characteristics and confounding variables (/2)	Total score (/14)
Kujawa, S. G., M. C. Liberman (2006). AOHCleration of age-related hearing loss by early noise exposure: evidence of a misspent youth. *J Neurosci,* 26(7): 2115–2123.	0	2	1	2	1	2	2	**10**
Kujawa, S. G., Liberman, M. C. (2009). Adding insult to injury: cochlear nerve degeneration after “temporary” noise-induced hearing loss. *The Journal of Neuroscience*, *29*(45), 14077–14085.	0	2	1	2	1	2	2	**10**
Lee, F. S., Matthews, L. J., Dubno, J. R., Mills, J. H. (2005). Longitudinal study of pure-tone thresholds in older persons. *Ear and Hearing*, *26*(1), 1–11.	0	1	2	2	2	1	1	**9**
Liberman, M. C., Epstein, M. J., Cleveland, S. S., Wang, H., Maison, S. F. (2016). Toward a differential diagnosis of hidden hearing loss in humans. *PloS One*, *11*(9), e0162726.	0	1	1	2	2	2	2	**10**
Lin, H. W., Furman, A. C., Kujawa, S. G., Liberman, M. C. (2011). Primary neural degeneration in the Guinea pig cochlea after reversible noise-induced threshold shift. *Journal of the Association for Research in Otolaryngology*, *12*(5), 605–616.	0	2	1	2	2	2	2	**11**

	Randomization (/2)	Similar groups (/2)	Inclusion and exclusion criteria (/2)	Results measured in a standard and valid way (/2)	Analysis strategies adequately described (/2)	Subjects excluded described completely (/2)	Control of demographic characteristics and confounding variables (/2)	Total score (/14)
Maison, S.F., Usubuchi, H., Liberman, M.C. (2013). Efferent feedback minimizes cochlear neuropathy from moderate noise exposure. *J. Neurosci.* 33, 5542–5552.	0	2	1	2	2	2	2	**11**
Makary, C. A., Shin, J., Kujawa, S. G., Liberman, M. C., Merchant, S. N. (2011). Age-related primary cochlear neuronal degeneration in human temporal bones. *Journal of the Association for Research in Otolaryngology*, *12*(6), 711–717.	0	2	2	2	2	2	1	**11**
Mehraei, G., Hickox, A. E., Bharadwaj, H. M., Goldberg, H., Verhulst, S., Liberman, M. C., Shinn-Cunningham, B. G. (2016). Auditory Brainstem Response Latency in Noise as a Marker of Cochlear Synaptopathy. *The Journal of Neuroscience*, *36*(13), 375–53764.	0	2	2	2	2	2	2	**12**
Prendergast, G., Guest, H., Munro, K. J., Kluk, K., Léger, A., Hall, D. A., ..., Plack, C. J. (2016). Effects of noise exposure on young adults with normal audiograms I: Electrophysiology. *Hearing Research,344,* 68–81.	0	1	1	2	2	1	2	**9**
Rosenhall, U. (2003). The influence of ageing on noise-induced hearing loss. *Noise and Health*, *5*(20), 47.	0	1	0	2	1	1	1	**6**

	Randomization (/2)	Similar groups (/2)	Inclusion and exclusion criteria (/2)	Results measured in a standard and valid way (/2)	Analysis strategies adequately described (/2)	Subjects excluded described completely (/2)	Control of demographic characteristics and confounding variables (/2)	Total score (/14)
Sergeyenko, Y., Lall, K., Liberman, M. C., Kujawa, S. G. (2013). Age-related cochlear synaptopathy: an early-onset contributor to auditory functional decline. *The Journal of Neuroscience*, *33*(34), 13686–13694.	0	2	1	2	1	2	2	**10**
Song, Q., Shen, P., Li, X., Shi, L., Liu, L., Wang, J., ..., Wang, J. (2016). Coding deficits in hidden hearing loss induced by noise: the nature and impacts. *Scientific Reports*, *6*.	0	2	1	2	2	2	2	**11**
Stamper, G. C., Johnson, T. A. (2015a). Auditory function in normal-hearing, noise-exposed human ears. *Ear and Hearing*, *36*(2), 172.	0	1	1	2	2	1	2	**9**
Stamper, G. C., Johnson, T. A. (2015b). Letter to the Editor: Examination of Potential Sex Influence on Auditory Function in Normal-Hearing, Noise-Exposed Human Ears, *Ear and Hearing, 36*(2), 172.	0	1	1	2	2	1	2	**9**
Viana, L. M., O'Malley, J. T., Burgess, B. J., Jones, D. D., Oliveira, C. A., Santos, F., ..., Liberman, M. C. (2015). Cochlear neuropathy in human presbycusis: Confocal analysis of hidden hearing loss in post-mortem tissue. *Hearing Research*, *327*, 78–88.	0	2	1	2	1	2	1	**9**

	Randomization (/2)	Similar groups (/2)	Inclusion and exclusion criteria (/2)	Results measured in a standard and valid way (/2)	Analysis strategies adequately described (/2)	Subjects excluded described completely (/2)	Control of demographic characteristics and confounding variables (/2)	Total score (/14)
Wang, Y., and Ren, C. (2012). Effects of repeated “benign” noise exposures in young CBA mice: shedding light on age-related hearing loss. *Journal of the Association for Research in Otolaryngology*, *13*(4), 505–515.	1	2	1	2	2	2	2	**12**
Xiong, M., Yang, C., Lai, H., Wang, J. (2014). Impulse noise exposure in early adulthood accelerates age-related hearing loss. *European Archives of Oto-Rhino-Laryngology*, *271*(6), 1351–1354.	1	1	1	2	2	1	0.5	**8.5**