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LITERATURE REVIEW

Combined exposure to noise and ototoxic substances

European Agency for Safety and Health at Work

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COMBINED EXPOSURE TO NOISE AND OTOTOXIC SUBSTANCES

Authors:

Pierre Campo, Katy Maguin, Institut National de Recherche et de Sécurité pour la prévention des accidents du travail et des maladies professionnelles – INRS, France

Stefan Gabriel, Angela Möller, Eberhard Nies, Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung – BGIA, (Institute for Occupational Safety and Health of the German Social Accident Insurance), Germany

María Dolores Solé Gómez, Instituto Nacional de Seguridad e Higiene en el Trabajo – INSHT (Spanish National Institute for Safety and Hygiene at Work), Spain

Esko Toppila, Työterveyslaitos Institutet for Arbetshygien (Finnish Institute of Occupational Health – FIOH), Finland

Members of the Topic Centre Risk Observatory

Edited by:

Eusebio Rial González, European Agency for Safety and Health at Work (EU-OSHA)

Joanna Kosk-Bienko, European Agency for Safety and Health at Work (EU-OSHA)

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Table of Contents

List of figures and tables:

1. Introduction

1.1. Scope and objectives

The fact that loud noise has deleterious effects on auditory function is well documented and widely recognised. According to the European Risk Observatory Report "Noise in Figures" published by the European Agency for Safety and Health at Work (EU-OSHA, 2006), noise-induced hearing loss is one of the most prominent occupational diseases in Europe. The report, however, clearly states that noise is no longer perceived as the only source of work-related hearing damage and concludes that more attention is required to the matter of combined risks for workers exposed to high-level noise with work-related substances.

Avicenna (Abu Ali al-Husayn ibn Abd-Allah ibn Sina Balkhi), the Persian philosopher and medical scholar, is considered the first person to describe the harmful effect of a chemical substance on ear function. In his most influential Canon of Medicine, completed almost 1,000 years ago, he warned that when mercury vapour was used to combat head lice, the host could be deafened by the treatment. In the 19th century the antimalarial drugs quinine and chloroquine as well as the anti-inflammatory salicylates became known as inducers of temporary ear impairments. More recently, in the mid-20th century, hearing impairment caused by streptomycin and other antibiotics prompted pharmacologists and toxicologists to carry out deeper research into the action of so-called ototoxic substances, which can affect the structures and/or the function of the inner ear and the associated signal transmission pathways in the nervous system (Schacht & Hawkins, 2006).

Yet, it was essentially not until the 1970s, when the ototoxicity of several industrial chemicals including solvents was recognised, that ototoxic substances came gradually to the attention of occupational hygienists. In 1986, Bergström & Nyström published the remarkable results of an epidemiological follow-up study in Sweden, which had been started in 1958 and embraced regular hearing tests in workers. Interestingly, a large proportion of employees in a chemicals division suffered from hearing impairment although noise levels were significantly lower than those in sawmills and paper pulp production. The authors suspected industrial solvents of being an additional causative factor of hearing loss.

Workers are commonly exposed to multiple agents. Physiological interactions with some mixed exposures can lead to an increase in the severity of a harmful effect. This applies not only to the combination of interfering chemical substances but in certain cases to the co-action of chemical and physical factors as well. Hence, it is obvious that the effects of ototoxic substances on ear function can be aggravated by noise, which remains a well-established cause of hearing impairment.

In two expert forecasts published by the European Agency for Safety and Health at Work (EU-OSHA, 2005a, 2009) the item "combined effects of chemical hazards with physical hazards (e.g. ototoxic products and noise)" was consistently rated as an emerging risk. Moreover, a review of various national, EU and international sources identifying future research needs in the field of occupational safety and health confirmed that "many workers are exposed to a combination of low-dose substances that interact with other occupational risks such as noise, vibration, radiation and psychosocial factors" (EU-OSHA, 2005b).

According to the Fourth European Working Conditions Survey of the European Foundation for the Improvement of Living and Working Conditions (Parent-Thirion et al., 2007), approximately 30% of the EU-27 workers in 2005 report exposure to noise at least a quarter of the time at the workplace, 11.2% the inhalation of vapours such as solvents and thinners, 19.1% the inhalation of smoke, fumes, powder or dust and 14.5% the handling of chemical substances.

The Agency's report "Noise in Figures" (EU-OSHA, 2006) explicitly mentions the following tasks and industries as harbouring potential for the hazardous combined exposure to noise and chemicals: printing, painting, shipbuilding, construction, glue manufacture, metal products, chemicals, petroleum, leather products and furniture-making, agriculture and mining.

The present publication aims to provide the European Risk Observatory target audience – researchers and policy-makers – with a comprehensive picture of our knowledge concerning the hazards of the combined workplace exposure to noise and chemical substances that may affect workers' hearing. This task is to be achieved by:

- describing the basic features of the physiological mechanisms leading to hearing impairment,
- presenting current diagnostic tools,
- identifying in the scientific literature chemicals that can be deleterious to the inner ear,
- ranking the certainty of the ototoxic properties claimed for them in a defined weight-of-evidence approach,
- describing known combined health effects resulting from exposure to multiple ototoxic substances and in particular from the interaction of ototoxic substances and noise,
- pointing out the work areas where exposure to ototoxic substances is likely,
- addressing gaps in the knowledge for proposed future action and research,
- highlighting national and European policies for the reduction of risks relating to ototoxic substances and combined exposure.

1.2. Hearing mechanism: from sounds to nerve impulses

Hearing is a complex mechanism, which implies a peripheral receptor, the ear, and an integrating centre in the brain, the auditory cortex.

Sound pressure fluctuations are amplified by the external ear and make the tympanic membrane (ear drum) vibrate (Figure 1). The tympanic vibrations are transmitted to a chain of three ossicles: malleus ("hammer"), incus ("anvil") and stapes ("stirrup"). The displacements of the footplate of the stapes inside the oval window of the cochlea (auditory part of inner ear) produce volume displacements of the cochlear liquids (perilymph and endolymph), which make the organ of Corti vibrate. The mechanical deformation of the organ of Corti is in fact the starting point of the neurosensory hearing process. The organ of Corti contains hair cells having a mechano-sensitive hair bundle (i.e. stereocilia) on their apical surface. Displacements of the bundle tip by just a few nanometres provoke the release of neurotransmitters onto the contacting auditory fibres. Then, the nervous impulses are conveyed via the auditory nerve (afferent auditory fibres) up to the auditory cortex located within the temporal lobe of the brain, where they are decoded as auditory messages. Essential for the normal function of hair cells is the endocochlear potential, which is generated by the stria vascularis, a layer of highly vascular cells on the outer wall of the cochlear duct.

Figure 1: Schematic section of human ear

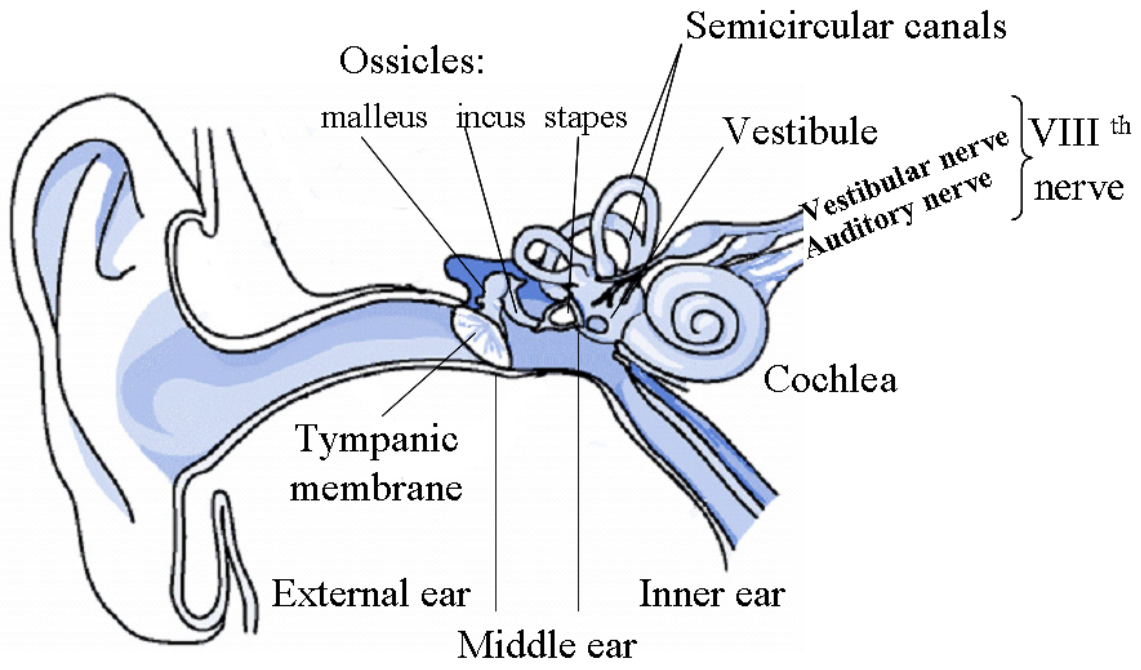
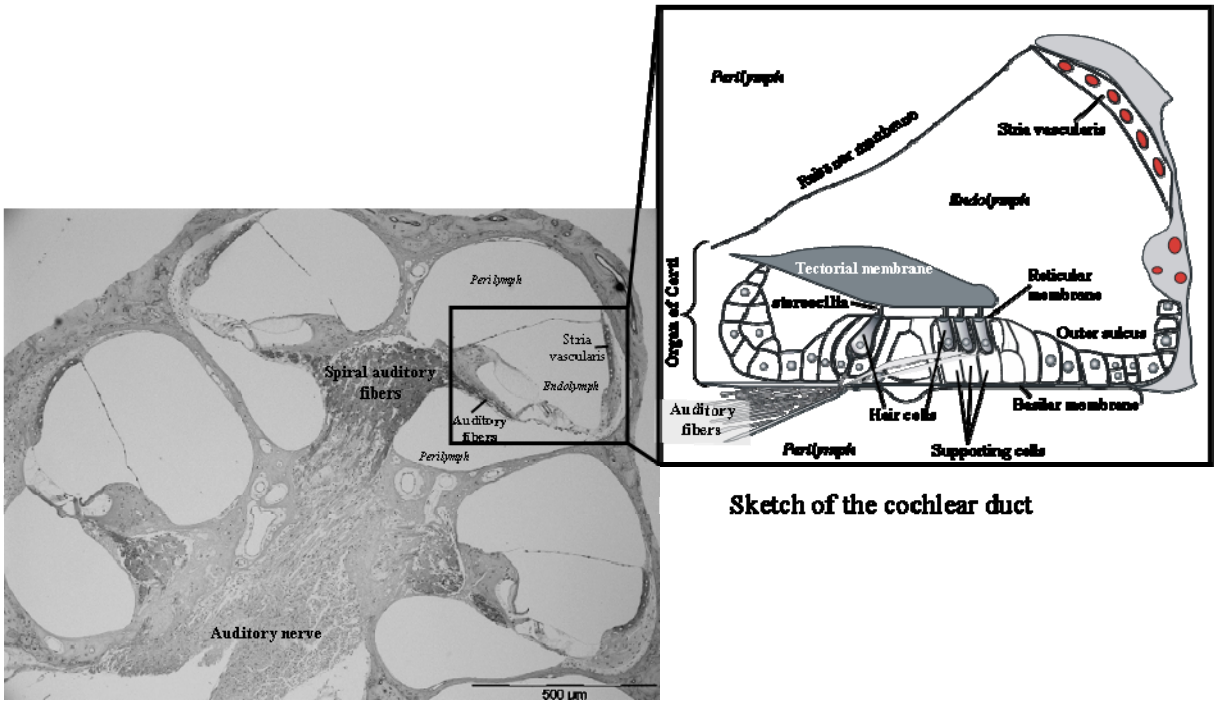


Figure 2: Cross section of the cochlea and drawing of the cochlear duct.



Sketch of the cochlear duct

Cross-section of the cochlea

1.3. Hearing hazards: definitions

Basically, hearing impairment corresponds to a dysfunction of the auditory receptor, the cochlea (Figures 1 and 2) and more rarely, to the auditory neural pathways. The characteristics are a bilateral decrease in hearing sensitivity: a loss of frequency discrimination and a loss of speech intelligibility in a noisy environment. Besides age-related auditory deficits (presbycusis), there are environmental factors that can induce hearing dysfunctions. Among them, the most prominent and recognised occupational factor which affects hearing is noise. However, exposure to certain chemical substances may harm hearing as well.

1.4. Noise

By and large, noise is a collection of sounds. Basically the notion of noise refers to an annoying sensation that can nevertheless be informative (alarm, horn, scream). Noise is a sound generated by air vibrations. Each sound is characterised by its frequency (basic unit: hertz or Hz; 1 Hz is equal to one cycle per second) and by its intensity, the latter expressed on a logarithmic scale relative to a specified reference level as “sound pressure level” (dB SPL, “dB” stands for “decibel”). In order to approximate the human ear's response to low-level sound, defined weighting filters are applied. Usually the occupational noise intensity is measured in so-called A-weighted decibels (dB(A)) to take the human ear’s sensitivity into account.

It is well known that occupational noise (broadband noise) may induce a rise in the auditory threshold in the 3 to 5 kHz (“kHz” means “kilohertz” or 1000 Hz) range of frequencies. This auditory deficit is called a “notch” (Gravendeel & Plomp, 1959). It depends on the interaction of noise parameters such as frequency, intensity, duration of exposure (acute vs chronic), nature of the noise (e.g. continuous, impulsive, intermittent), distance of the worker from noisy sources, workplace conditions (close or open field), and individual factors such as individual sensitivity, age, etc. Auditory threshold shifts may be reversible or irrreversible (temporary threshold shifts (TTS) or permanent threshold shifts (PTS); Nordmann, Bohne & Harding, 2000).

TTS or auditory fatigue is due to glutamatergic excitotoxicity (see glossary) underneath the cochlear hair cells and/or to an energetic exhaustion of the hair cells (Liberman & Mulroy, 1982; Robertson, 1983). Recovery is possible, depending on the post-exposure rest.

If a residual auditory threshold shift lasts for four weeks after exposure, the impairment is considered permanent (Salvi, Henderson & Eddins, 1995). PTS results from irreversible lesions which predominantly occur within the organ of Corti (Figure 2; Borg, Canlon & Engström, 1995; Liberman & Dodds, 1987; Liberman & Mulroy, 1982).

Two distinct mechanisms of PTS may take place in the organ of Corti, i.e. mechanical and metabolic damage (Figure 3; Saunders, Dear & Schneider, 1985);

- Mechanical damage

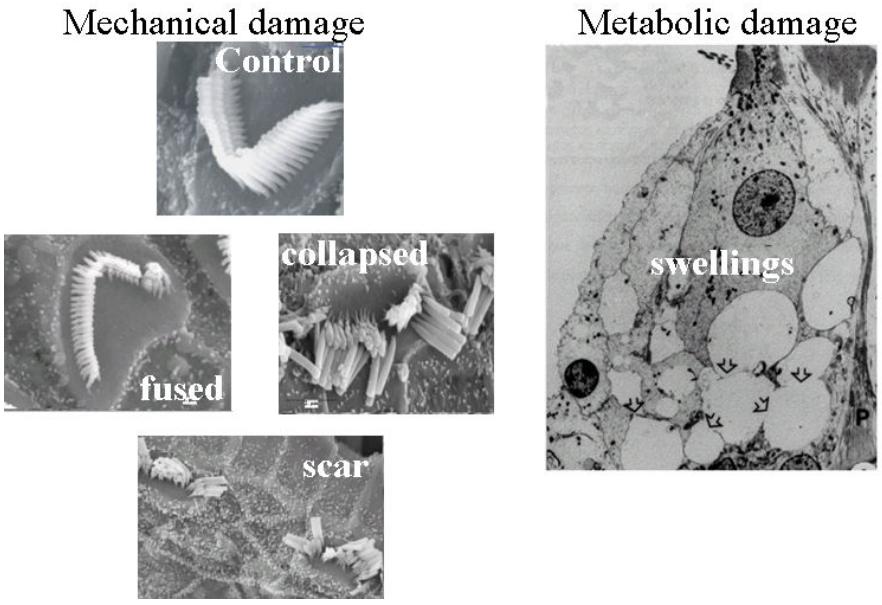
  Impulsive occupational noise produced by pneumatic drills for instance, can induce mechanical damage such as:

  - broken, collapsed, fused or floppy stereociliae of the cochlear hair cells (Figure 3, left; Engström, Borg & Canlon, 1986; Nordmann, Bohne & Harding, 2000),
  - micro-lesions of the plasma membrane of cochlear hair cells (Mulroy, Henry & McNeil, 1998),
  - and tears in Reissner's or the reticular membrane (Bohne & Rabitt, 1983; Hamernik, Turrentine & Roberto, 1986).

- Metabolic damage

  Prolonged exposure to noise can cause metabolic damage due to (1) the excitotoxic phenomenon leading to acute swellings (Figure 3, right; Puel et al., 1995; Ruel et al., 2007) and (2) the generation of reactive oxygen species at the level of the sensory cells of the organ of Corti (Henderson et al., 2006; Kaygusuz et al., 2001).

Figure 3: Left insert: Scanning electron micrographs of rat hair cells, showing typical mechanical damage induced by noise (extract from INRS data). Right insert: Transmission electron micrograph of a guinea pig hair cell, showing typical swellings induced by noise (extract from Puel et al., 1995).



According to Hamernik et al. (1993), the development of a metabolic rather than a mechanical mechanism might be associated more with the noise intensity than with the nature of the noise. Thus,

a relationship would exist between a “critical intensity” and the development of the one or other mechanism (Spoendlin, 1985). From a theoretical point of view, above the “critical level”, the stresses developed within the organ of Corti would exceed the elastic limits of the tissues, so that the damage would be purely mechanical and could arise even for noise of very short duration. Below the “critical level”, the pathology of the organ of Corti would tend to be metabolic.

1.5. Chemicals

While noise is considered a physical factor for damage to the cochlea, chemical substances can impair the cochlea, the vestibulo-cochlear apparatus, the eighth cranial nerve or the central nervous system.

1.5.1. Neurotoxicants

All substances which may affect the central or peripheral nervous system can be considered neurotoxic. Neurotoxic substances may be ototoxic (Fuente & McPherson, 2007; Lazar et al., 1983). For instance, some organic solvents have adverse effects on auditory, optic and vestibular nerve fibres (Gatley, Kelly & Turnbull, 1991; Greenberg, 1997; Tham et al., 1990). Heavy metals or compounds thereof such as mercury (Gopal, 2008), trimethyltin (Hoeffding & Fechter, 1991) or lead (Yamamura et al., 1989) can induce deafness among other symptoms. Carbon monoxide is believed to be neurotoxic and ototoxic because of the hypoxia induced by this gas (Makishima et al., 1977).

1.5.2. Ototoxicants

All substances that may affect the structures and/or the function of the inner ear (auditory plus vestibular apparatus) and the connected neural pathways can be considered ototoxic. In other words, both cochleotoxicants and vestibulotoxicants can be defined as ototoxicants.

1.5.3. Cochleotoxicants

A cochleotoxicant is a chemical substance conveyed by blood up to the cochlea that impairs the cochlear structures including the auditory sensory cells (“hair cells”), the fluid-producing cell layer on the outer wall of the cochlear duct (“stria vascularis”) and the starting point of the auditory nerve, the spiral ganglion cells. In most cases, the cochlear hair cells are the primary targets of cochleotoxicants. Antitumour drugs (Macdonald et al., 1994; Hamers et al., 2003) and aminoglycosides (Forge & Schacht, 2000) are typical cochleotoxicants. On the other hand, there are cochleotoxic substances that may have temporary effects. For instance, diuretics (Forge, 1982) and salicylic acid (Bonding, 1979) can cause TTS by modifying the function of the stria vascularis.

1.5.4. Vestibulotoxicants

A vestibulotoxic substance may impair the structures and/or the function of the vestibular organ of the inner ear, thus affecting the sense of spatial orientation, body balance and movement control. Among these substances, streptomycin and gentamicin are two antibiotics well known for inducing vestibular hair cell degeneration (Selimoğlu, Kalkandelen & Erdoğan, 2003). In addition to antibiotics, some nitriles are known to induce vestibular dysfunction and loss of vestibular hair cells (Soler-Martín et al., 2007). Vestibular toxic effects may be among others dizziness, vertigo, equilibrium disorder, staggering gait or nystagmus (rapid involuntary eye movements).

1.6. Age

Presbycusis (or presbyacusis) refers to a constellation of age-related physiological degenerations associated with age-related disorders (elevated blood pressure, cholesterol levels, reactive oxygen species formation, oxidative stress, inherited and acquired mutations in the mitochondrial DNA; Brant et al., 1996; Liu & Yan, 2007; Rosenhall et al., 1993).

By and large, the effects of presbycusis are characterised by a bilateral loss of hearing sensitivity ranging from high to low audiometric frequencies and by a decreased ability to understand speech, particularly in the presence of background noise (Gilad & Glorig, 1979; Working Group of Speech Understanding and Aging, 1988). From a histopathological point of view, four predominant types of presbycusis can be identified (Schuknecht & Gacek, 1993):

- sensory presbycusis, which refers to the loss of sensory hair cells and supporting cells in the cochlea (Figure 2),
- neural presbycusis, which refers to degeneration of nerve fibres (Figure 2) in the cochlea and central neural pathways,
- strial presbycusis, which results from degeneration of the stria vascularis (Figure 2) in the cochlea,
- mechanical presbycusis which results from morphological changes of the basilar membrane of the cochlea (Figure 2).

At younger ages (<50 years) the first effects of presbycusis are normally concealed by (1) a central counterbalancing mechanism and (2) a particular compensating property of the organ of Corti.

1. The central nervous system and especially the brain exhibit a certain plasticity. Thus, in case of a slight hearing impairment, the brain would be capable of counterbalancing a decrease in the inputs coming from the inner ear in order to ensure a suitable level of excitability of the auditory nerve cells (Salvi, Wang & Powers, 1996; Willot & Lu, 1982).
2. Younger people possess more cochlear hair cells than necessary for ensuring normal hearing (“redundancy of hair cells”). As a result, a limited loss of hair cells can be afforded without leading to significant hearing deficits (Prosen et al., 1990).

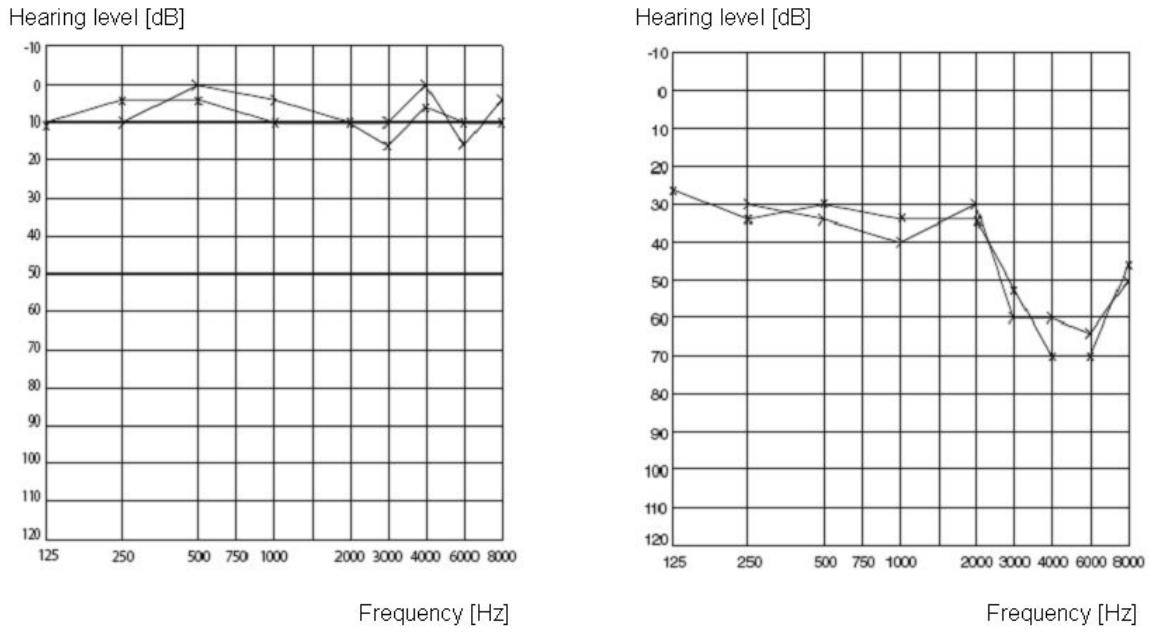
When a patient suffers from presbycusis earlier than can be expected for his or her age, the term “early presbycusis” may be applied.

2. Evaluation of hearing impairment

2.1. Pure tone audiometry

The gold standard in the evaluation of hearing is the pure tone audiogram (PTA). Although the human auditory range is from 20 to 20,000 Hz, the PTA in a strict sense only covers the speech spectrum: 250, 500, 1,000, 2,000, 3,000, 4,000, 6,000 and 8,000 Hz. The PTA is set out with frequency in hertz (Hz) on the horizontal axis and a dB hearing level (HL) scale on the vertical axis (Figure 4) representing in a standard way a person's hearing threshold level (lowest hearing level at which a tone is heard compared to the average threshold of hearing registered as 0 dB in the audiometer). For example, a threshold of 60 dB hearing level at 4000 Hz means that the person needs a tone intensity of 60 dB above the average normal hearing at 4000 Hz to hear the stimulus. The range for normal hearing is 0-25 dB HL (ISO 1999-1990). Nevertheless some subjects may have better-than-average hearing resulting in minus figures (e.g., - 15 dB).

Figure 4: PTAs for normal (left) and a "typical" noise-induced hearing loss (right). (Fig. provided by INSHT)



PTA classification gives no information on retrocochlear and central effects, makes no distinction between different causes and is a late indicator of auditory dysfunction. As noise-induced hearing loss (NIHL) may be exacerbated by concurrent exposure to ototoxic agents, medical surveillance of workers exposed to both agents needs to consider the use of more sensitive tests for hearing evaluation, from the cochlea to the higher auditory centres. These tests used in addition to PTA should help to localise the lesion site throughout the signal transmission chain from the ear to the higher auditory centres, to distinguish between the effects of noise and chemicals, to describe related pathologies, to identify susceptible workers, to make a differential diagnosis, etc.

Some of the tests suggested by the experts (Morata & Little, 2002; Morata, 2003; Sataloff & Sataloff, 1993) are the following:

2.2. High-frequency audiometry

High-frequency audiometry (HFA) is nearly the same as conventional audiometry (PTA) but includes frequencies ranging from 9 to 20 kHz. In some studies (Fausti et al., 1981; Fausti et al., 2005; Corliss, Doster & Simonton, 1970) noise was reported to initially affect frequencies above 8,000 Hz (mainly 10,000 to 16,000 Hz, before any gap in PTA is observed). Thus, HFA has been considered an early indicator of hearing impairment due to noise, ototoxicants or both and as a possible predictor of shifts

in conventional PTA (Ahmed et al., 2001; Bauman, 2003; Morata & Little, 2002; Tange, Dreschler & van der Hulst, 1985).

Other studies (e.g. Osterhammel, 1979; Laukli & Mair, 1985) found no difference in the effect of noise on hearing loss at very high frequencies between industrial workers exposed to steady-state noise and non-exposed controls. Results of Schwarze, Notbohm & Gärtner (2005) do not indicate that a loss of hearing capacity of very high pitches may give relevant information on the possible risk of the development of noise-induced hearing loss in the range of 1-6 kHz. The authors remarked, however, that the database was probably not adequate for a definite assessment of the suitability of the high-frequency audiogram for such an issue. Finally, one should bear in mind that high-frequency audiometry is a time-consuming method requiring skilled examiners, so that application in the context of routine health surveillance might lead to practical problems (Schwarze, Notbohm & Gärtner, 2005; Fausti et al., 2005).

2.3. Speech audiometry

Speech audiometry is based on the ratio of different speech units (syllables, multisyllable words, sentences, running discourse) presented at different sound levels to the proportion of speech units understood by the tested person. The number of speech units received correctly is plotted on a graph as a function of sound level. For normal ears, the curve of the speech audiogram is S-shaped and runs from a score of 0 to 100 percent. Three parameters characterise the speech audiogram: the position of the curve (Speech Reception Threshold (SRT)), i.e. the sound level at which the curve intercepts 50% or the sound level at which half the maximum score is reached); the slope of the curve; and the maximum score reached at a certain level (Speech Discrimination Score (SDS)).

SDS measures the ability to understand speech when it is amplified to a comfortable level. Speech discrimination is measured in percentage (100% = test person understands everything he/she hears; 80% = he/she understands in average 4 out of 5 words; 0% = he/she cannot understand a single word that is spoken, no matter how loud it is). Discrimination scores generally remain good (over 85%) in hearing loss caused by noise alone. People with retrocochlear hearing impairment caused by damage to the acoustic nerve and/or the auditory cortex in the brain usually present worse scores and even a decrease at the highest stimulus levels (roll-over).

2.4. Otoacoustic emissions

Otoacoustic emissions (OAEs) are sounds of cochlear origin (exclusively from outer hair cells amplifying the acoustic signals) that travel out through the middle ear and can be recorded by placing a small microphone inside the outer ear canal. Thus, the cochlea not only receives sounds, but also produces acoustic energy in form of low-level sounds that are re-emitted. Experimental studies suggest that outer hair cells amplify cochlear membrane motion 100 to 1,000 times (40 to 60 dB) and, as a by-product, produce various forms of OEAs (Kim et al., 1992). The absence of OAEs without middle ear pathology indicates sensory hearing impairment resulting from dysfunction of the outer sensory hair cells. Since OEAs are a sensitive measurement of outer hair cell integrity, they can be used to differentiate between sensory and neural/central hearing disorders and as early indicators of cochlear damage. Diagnostic OEA tests have been designed to provide a simple, efficient and non-invasive objective indicator of cochlear function.

There are two prominent types of OAE measurements: transient evoked otoacoustic emissions (TEOAEs) responding to wide-band click stimuli, and dual-tone evoked distortion product otoacoustic emissions (DPOAEs) that permit frequency discrimination. TEOAE and DPOAE techniques complement each other and were described to show high sensitivity to changes in cochlear status and even to temporary threshold shifts (Kemp, 2002). OAEs are normally very stable over time, and are thus suitable for monitoring changes in cochlear status. OAEs are expected to be present even in neural, central and psychogenic hearing impairments. The use of OAEs for the objective monitoring of the inner ear hearing function is meanwhile a clinical standard and works satisfactorily in particular if no clear changes in the pure tone audiometry are recognisable, although an initial onset of hearing disorders is anticipated. However, in a study aimed at evaluating the extent to which OAEs (i.e. TEOAE/DPOAE) may help better explain and verify the onset of noise-induced hearing loss and its progression, only a very weak correlation was found between hearing thresholds in PTA and OAE recordings. While TEOAEs are considered to be useful diagnostic tools for objectively determining

noise-induced hair cell loss, the pros and cons of DPOAEs are still under discussion (Ernst & Basta, 2006; Ernst & Basta, 2009). All in all, TEOAE recordings were found to be suitable objective noise tests, complementing but not entirely substituting PTA in preventive occupational health examinations of noise-exposed workers.

2.5. Brainstem auditory evoked potentials

Evoked potentials are electrical activities of the central nervous system (CNS) elicited by external stimuli. They permit the study of certain precise CNS functions and are commonly classified in terms of latency from stimulus onset. Brainstem auditory evoked potentials (BAEPs; short-latency components of auditory evoked potentials) are recordable following the presentation of a clicking sound in one ear, while the other ear is masked with “white noise” (i.e. noise whose frequencies have equal energy). This click causes the activation of the auditory nerve over about 10 milliseconds and generates a complex wave (amplitude) which relates to specific sites along the auditory pathway. This pattern is recorded by electrodes placed over the skull. BAEPs have been useful in studies of neurodegenerative diseases and of demyelinating processes. Demyelinating processes result in damage to the protective covering (myelin sheath) that surrounds nerves. When the myelin is damaged, nerve impulses slow down or even stop, causing neurological problems. BAEPs are also helpful in detecting injuries caused by ototoxic substances. BAEPs can reveal differences in hearing threshold, wave morphology, and/or latency in subjects receiving ototoxic agents, thereby indicating the occurrence of ototoxicity. Today, portable equipment is available for screening BAEPs, TEOAEs and DPOAEs, but has not been yet evaluated in occupational settings.

Table 1 summarises the tests and measurements used for the surveillance of hearing impairment:

Table 1: Tests and measurements used for the surveillance of hearing impairment

NAME	MAIN APPLICATIONS / ADVANTAGES
SUBJECTIVE TESTS	
Pure tone audiometry (PTA)	Ability to detect pure tones • Testing air and bone conduction thresholds. • Calculating hearing acuity. • Detecting significant threshold shifts. • Differentiating conductive hearing impairment (HI) from sensorineural HI. • Assessing hearing conservation programmes.
High-frequency audiometry (HFA)	Extension of PTA up to 20,000 Hz • From some specific results it has been concluded that high-frequency audiometry might be used as an early indicator of hearing loss. • Cost and time-constraints make HFA difficult to apply in occupational health surveillance.
Speech audiometry	Ability to discern and to understand speech in a quiet environment • Exclusion of such causes as Menière’s syndrome or acoustic neuroma. • Criterion for the recommendation of hearing aids.

NAME	MAIN APPLICATIONS / ADVANTAGES
OBJECTIVE TESTS	
Otoacoustic emissions (OAEs)	• Localising auditory defects of the cochlea. • Monitoring temporary or permanent changes in the cochlea (auditory fatigue; ototoxic effect; cochlear dysfunction).
Brainstem auditory evoked potentials (BAEPs)	• Detecting the hearing threshold. • Detecting sensorineural and retrocochlear impairments.

3. Consequences of hearing impairment for humans

Hearing impairment may comprise the following symptoms (Hétu, Getty & Hung, 1995):

- *Loss of hearing sensitivity* is observed on the audiogram. When the level of sound is below the individual's threshold of detection, it is not perceived.
- *Compressed loudness function*. In the frequency region where there is a loss of sensitivity, the rise in loudness as a function of sound level is somewhat distorted.
- *Loss of frequency resolution*. The ear cannot resolve two or more simultaneous sounds that are similar in frequency. This phenomenon, which has been extensively documented, is responsible for the most acutely felt effects of occupational hearing impairment, namely, the experience of hearing difficulties when there are competing signals. Loss of frequency selectivity is correlated with loss of sensitivity, and relatively large individual differences are also observed at comparable elevated hearing levels.
- *Loss of temporal resolution*. The ability to detect gaps in an ongoing sound is generally reduced when there is substantial loss of hearing sensitivity.
- *Loss of spatial resolution*. The ability to localise sound sources is reduced.
- *Persistent ongoing tinnitus* is relatively common among individuals with occupational hearing impairment, and it may impair concentration and interfere with rest and sleep. This, in turn, can result in a severe handicap (psychosocial disadvantages) because of the physical and psychological stress involved.

In the occupational environment, workers with hearing impairments require a signal-to-noise ratio (SNR, signal power relative to the noise power corrupting the signal) up to 25 dB higher than those needed by normal listeners for detecting, recognising and localising auditory warning sounds. Due to the characteristics of the warning signals in industry and of the necessity to wear hearing protection, workers with hearing impairments are more prone to accidents than workers with normal hearing. Because of a loss of frequency resolution, the SNR in communication needs to be 1-10 dB higher among hearing-impaired listeners than among normal-hearing individuals to achieve a given intelligibility score (Hétu, Getty & Hung, 1995; Plomp, 1986).

In daily communication, subjects with hearing impairments experience disabilities in verbal communication when exposed to less than ideal conditions, e.g. on the phone, varying levels of background noise, reverberant rooms, and in group conversations (Hallberg & Barrenäs, 1993; Hétu et al., 1995). Because the onset of hearing impairment is deceptive, people tend to avoid these disabling situations. In the long run, this avoidance process results in changes in the lifestyle of people with hearing impairments – changes characterised, in most cases, by serious self-imposed restrictions with regard to social participation. The experience of hearing disabilities may have a negative effect on self-image, which manifests itself as a sense of incompetence, perceiving oneself as physically diminished, prematurely old, or having a defect (Hallberg & Carlsson, 1991; Hétu, Getty & Hung, 1995).

The resulting handicap caused by occupational hearing impairment may affect the social and family life in different ways. The partner of a person with hearing impairment needs to pay attention when communicating with the impaired family member. The verbal contact should be performed under visual conditions and the information content must be confirmed. The handicap affects the unimpaired family members by forcing them to keep the conversations brief. Other consequences may include setting higher volumes when watching television or listening to music, speaking in a loud voice and the increased social dependence of the impaired partner (Hétu, Jones & Getty, 1993).

Modern production techniques call for improved communication skills even in noisy environments. In addition, frequent changes in production techniques necessitate ongoing training. This is difficult for people with hearing impairment, who therefore may have an increased risk of unemployment.

4. Ototoxic substances

4.1. Rating the weight of evidence

The assessment of industrial ototoxic chemicals stems predominantly from experimental findings obtained with animals. Epidemiological studies in various industries support these experimental findings. However, our knowledge of the ototoxic effects of industrial chemicals under exposure conditions prevalent at today's workplaces in Europe is poor. In animal studies that show evidence of the ototoxic effects of a compound, much higher exposure concentrations were applied than those found in current occupational settings. In several cases, the concern about the ototoxicity of industrial chemicals is exclusively based on animal studies, whilst supportive evidence from human studies is lacking. With regard to scientific findings in animals, the qualitative relevance to human health can basically be assumed providing there is no indication of a substantial difference in biological response (e.g. metabolism) when comparing test animals and humans.

The data given below are based on an extensive review of the research literature on this topic with respect to epidemiological data, animal studies, case reports and other relevant information. We propose a classification system for the assessment of the weight of evidence for ototoxic properties of a substance based on the methodological quality, quantity (magnitude of effect, numbers of studies from different centres or research groups, and sample size) and consistency of results (the extent to which similar findings are reported using similar and different study designs). Human data are given priority over animal data.

Overall, the following categories predominantly reflect the evidence of the qualitative ability of chemicals to induce ototoxic effects.

- The weight of evidence is classified as “good” (confirmed ototoxic substance) if it is obtained from at least two well-documented animal studies from different centres or research groups consistently reporting clear ototoxic effects in an overall coherent manner. If the data are particularly comprehensive and can be judged as reliable, the evidence obtained from a single research group is included in this category. If supporting human data are lacking, species-specific features must not provide indications contradicting the extrapolation of animal findings to humans.
- The weight of evidence is graded as “fair” (suspected ototoxic substance) if the results are to a certain extent conflicting, or there is a comparatively small body of information available, which nevertheless can be judged as reliable (e.g. one or two valid studies with one test animal species carried out in the same laboratory, supported by structure/activity relationship considerations or a reasonable mechanistic model).
- The weight of evidence is scored as “poor” (questionable ototoxic substance) if there is a limited indication from single or sporadic observations/case studies which cannot be judged in a qualitatively sufficient manner and/or confounding factors cannot be excluded.

4.2. Ototoxic compounds

4.2.1. Compounds with “good evidence” of ototoxicity

▪ *Pharmaceuticals*

Many drugs are recognised for their potential ototoxic side-effects:

- Antibiotics (chemotherapeutic agents inhibiting the growth of bacteria).
  - Aminoglycosides (e.g. streptomycin, dihydrostreptomycin, gentamycin, amikacin).
  - Certain other antibiotics (e.g. tetracycline antibiotics, erythromycin, vancomycin).
- Certain antineoplastics (antitumour drugs, e.g. cisplatin, carboplatin, bleomycin).
- Certain diuretics (drugs elevating the urine excretion, e.g. furosemide, ethacrynic acid, piretanide and bumetanide).
- Certain analgesics and antipyretics (painkillers and fever reducers: salicylates, quinine, chloroquine).

It is clear that aminoglycosides such as gentamicin, kanamycin, streptomycin, amikacin, tobramycin, and neomycin have cochleotoxic effects, the hair cells being particularly sensitive (Forge & Schacht, 2000; Govaerts et al., 1990; Hashino, Shero & Salvi, 1997). After administration, they can penetrate the cochlea through the stria vascularis (Govaerts et al, 1990; Tran Ba Huy et al., 1983) before reaching the cochlear hair cells in which they can be stored for several months (Aran et al., 1999; Dulon et al., 1993). Aminoglycoside-induced hearing loss spreads from high to low frequencies (Govaerts et al., 1990) depending on the duration of treatment and the dose.

Platinum-derivates such as cisplatin and carboplatin are antitumour drugs with ototoxic side-effects (Fausti, Schechter & Rappaport, 1984; Helson et al., 1978; Macdonald et al., 1994; Montaguti et al., 2002). The ototoxicity induced by platinum-derivates is characterised by loss of cochlear hair cells and cells of the spiral ganglion (agglomeration of nerve cell bodies in the cochlea) and degeneration of the stria vascularis (Hamers et al., 2003). As for aminoglycosides, hearing impairment induced by platinum-derivates spreads from high to low frequencies (Van der Hulst, Dreschler & Urbanus, 1988).

Ethacrynic acid, furosemide and bumetanide are so-called loop diuretics (acting on the ascending limb of the “loop of Henle” in the kidney), which inhibit sodium and chloride ion reabsorption. They are widely used in current clinical treatments. Their ototoxicity is a significant side-effect, which may last during treatment. Their cochleotoxic effect is characterised by a sudden high-frequency hearing loss due to dysfunctions of the stria vascularis (Ding et al., 2002; Forge, 1982; Martínez-Rodríguez et al., 2007).

The ototoxic effects of loop diuretics seem to be associated with the stria vascularis, which is affected by changes in the ionic gradients between the perilymph and endolymph. These changes cause edema of the epithelium of the stria vascularis. Evidence also suggests that endolymphatic potential is decreased; however, this is usually dose-dependent and reversible.

Ototoxicity caused by ethacrynic acid seems to develop more gradually and takes longer to resolve than that caused by furosemide or bumetanide. Overall, ototoxicity attributed to this group of medications is usually self-limited and reversible in adult patients, although irreversible hearing loss has been reported in neonates (Mudd et al., 2008).

The adverse effects of certain non-steroid analgesic drugs on hearing are well documented in the literature. High doses of salicylate (> 2.5g/d) induce an auditory temporary threshold shift and sometimes tinnitus (McCabe & Dey, 1965; Myers & Bernstein, 1965; Stypulkowski, 1990). In general the recovery to a normal auditory sensitivity occurs within two or three days from the last salicylate administration. The exact mechanism of salicylate-induced hearing impairments is still uncertain. It seems that the ototoxic effects result from a conjunction of several reversible disturbances at the level of the cochlea (Cazals et al., 1988; Douek, Dodson & Bannister, 1983; Stypulkowski, 1990).

▪ *Solvents*

“Good evidence” (at least in animal studies) has been accumulated on the adverse effects on hearing of the following solvents:

- Toluene, ethylbenzene, n-propylbenzene,
- Styrene and methylstyrenes,
- Trichloroethylene,
- p-Xylene,
- n-Hexane,
- Carbon disulfide.

From a mechanistic point of view, solvent-induced hearing impairments in humans would suggest the involvement of both the inner ear and the central nervous system (Fuente & McPherson, 2006; Gopal, 2008). There are also indications of central balance disorders caused by organic solvents (Fuente et al., 2006; Gopal, 2006; Möller et al., 1990; Ödkvist et al., 1987; Toppila et al., 2006).

The cochleotoxic effects of aromatic solvents such as toluene, styrene, ethylbenzene, p-xylene, various methylstyrenes, allylbenzene and n-propylbenzene have been demonstrated in numerous animal experiments (Campo et al., 2001; Cappaert et al., 1999, 2000; Crofton et al., 1994; Gagnaire

& Langlais, 2005; Mattsson et al., 1990; Pryor et al., 1983, Pryor, Rebert & Howd, 1987; Rebert et al., 1983). It has been shown that exposure to these solvents can provoke irreversible hearing impairment, the cochlear hair cells being considered a target tissue for these solvents (Figure 5; Campo et al., 1997; Johnson & Canlon, 1994; Sullivan, Rarey & Connolly, 1988). Unlike p-xylene, o-xylene and m-xylene showed no ototoxicity (Campo et al., 2001; Cappaert et al., 1999, 2000; Crofton et al., 1994; Mattsson et al., 1990; Pryor et al., 1983; 1987; Rebert et al., 1983).

Most of the studies on aromatic solvents have been performed with rats. The rat cochlea is sensitive to aromatic solvents contrary to that of guinea pig or chinchilla (Campo, Lataye & Bonnet, 1993; Cappaert et al., 2002; Davis et al., 2002; Fechter, 1993). These findings have been attributed to metabolic and other toxicokinetic differences (Campo et al., 2006; Davis et al., 2002; Gagnaire et al., 2007a). Because of their metabolism, rats are considered comparatively good animal models for the investigation of the ototoxic properties of aromatic solvents in humans (Campo & Maguin, 2006; Kishi et al., 1988).

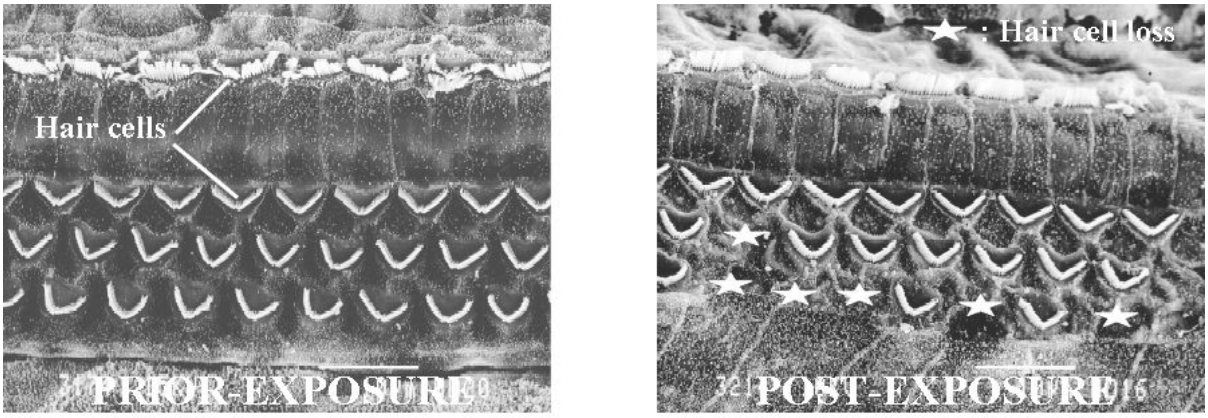
The most likely scenario of the toxic process of aromatic solvents is a chemical poisoning of hair cells resulting in disorganisation of their membranous structures (Campo et al., 2001). This may trigger the death of these cells (Figure 5; from Lataye, Campo & Loquet, 1999). The loss of hair cells is irreversible because the organ of Corti is not able to replace the neurosensorial cells.

Concerning the non-aromatic solvents, exposure to high concentrations of trichoroethylene has been shown to disrupt cochlear sensory hair and spiral ganglion cells as well, i.e. the auditory nervous pathways within the cochlea (“cochlear dysfunction”; Albee et al., 2006; Crofton & Zhao, 1993; Fechter et al., 1998; Prasher et al., 2004; for review see Vyskocil et al., 2008a). By contrast, the exposure of animals to carbon disulfide and n-hexane has been shown to affect the auditory nervous pathway beyond the cochlea (“retrocochlear dysfunction”; Johnson & Nylen, 1995; Hirata et al. 1992a; Howd et al., 1983; Rebert and Becker, 1986; for review see Vyskocil et al., 2008b).

Epidemiological and experimental investigations in humans dealing with solvent-induced hearing impairments since the mid-eighties of the last century mainly focused on occupational exposure to styrene, toluene, solvent mixtures and carbon disulfide (Abbate et al., 1993; Chang et al., 2003, 2006; Hirata et al., 1992b; Johnson et al., 2006; Kaufman et al., 2005; Kim et al., 2005; Mascagni et al., 2007; Morata, 1989; Morata & Dunn, 2004; Morata et al., 1993, 2002; Morioka et al., 1999; Rabinowitz et al., 2008; Sliwinska-Kowalska, 2005; Sulkowski et al., 2002). Epidemiological studies investigate the relationship between the occupational exposure to a solvent and the occurrence of hearing impairments. Hearing thresholds were determined by pure tone audiometry, the determination of frequency range limits, otoacoustic emissions, evoked potentials, speech discrimination tests (see chapter 3) and others. On the whole, studies on employees in various branches of industry gave inconsistent results. Indeed, a clear relationship between solvent and hearing impairment is difficult to assess with epidemiological studies, given the complexity of the workplace environment where noise and solvents can be simultaneously present (for example, see critical review of Lawton, Hoffmann & Triebig, 2006; Hoet & Lison, 2008). Quite often the workers were exposed to various substances. Furthermore, most of these studies had a cross-sectional design that featured a number of weaknesses in the interpretation of the findings. For instance, chronic effects were related to currently measured exposures. In some cases, the exposure concentrations measured at the time of the study were markedly lower than those ascertained in past years (Morata et al. 1993).

All in all, there are no clear data on dose-response relationships nor clear effects on auditory thresholds in humans (for reviews see: Lawton, Hoffmann & Triebig, 2006; Hoet & Lison, 2008; Vyskocil et al., 2008a and b). Further human studies are needed for clarification of these issues. However, in the interim, one cannot rule out a likely relationship between solvent exposure and hearing impairments.

Figure 5: **Scanning electron micrograph of a rat organ of Corti prior to (left panel) and after (right panel) toluene exposure (extract from Lataye, Campo & Loquet, 1999).**



▪ *Asphyxiants*

The ototoxicity of

- carbon monoxide and
- hydrogen cyanide and its salts (cyanides).

is believed to be a consequence of effective oxygen deprivation (hypoxia) within the cochlea. In human studies and animal experiments, carbon monoxide (Fechter, Thorne & Nutall, 1987; Goto, Miyoshi & Yoshitomo, 1972; Liu & Fechter, 1995) or cyanide exposures (Evans & Klinke, 1982; Konishi & Kelsey, 1968; van Heijst et al., 1994) have been shown to impair the cochlear function only under severe exposure conditions. At low concentrations, they have reversible auditory effects. The findings of experimental studies carried out with laboratory animals showed that these asphyxiants have predominant effects on high-frequency tones and suggested that, while cyanides induce a dysfunction of the stria vascularis (Konishi & Kelsey, 1968; Tawackoli, Chen & Fechter, 2001), carbon monoxide produces excessive glutamate release (glutamatergic excitotoxicity) in the synaptic area underneath the inner hair cells (Kanthasamy et al., 1994; Liu & Fechter, 1995).

▪ *Nitriles*

The nitriles for which an ototoxic effect has been demonstrated in animals include:

- Acrylonitrile,
- 3,3'-Iminodipropionitrile,
- 3-Butenenitrile,
- cis-2-Pentenenitrile,
- cis-Crotononitrile.

Cis-2-pentenenitrile, 3-butenenitrile, cis-crotononitrile and 3,3'-iminodipropionitrile were shown to cause permanent impairment of hearing (cochlear hair cell loss plus spiral ganglion cell loss for the latter) and balance (vestibular sensory hair cell loss) in the inner ears of rats, mice, guinea pigs and frogs (Balbuena & Llorens 2001, 2003; Crofton et al. 1994; Gagnaire & Marignac, 1999; Gagnaire et al. 2001b; Soler-Martín et al. 2007).

By contrast, acute acrylonitrile exposure in rats has been shown to produce transient loss in auditory sensitivity specifically in the high-frequency range (Fechter et al., 2003). While the effects of chronic acrylonitrile exposure have not been studied yet, we cannot rule out the possibility that higher doses might also produce permanent hearing impairments like the nitriles previously cited. Because of its structural relationship with the more thoroughly investigated nitriles and some evidence of worsening

the described ototoxic effects of noise (see chapter 5.2.4), we recommend treating acrylonitrile as an ototoxic substance.

▪ *Metals and metal compounds*

Ototoxic properties have been demonstrated for compounds of the following metals:

- Lead and lead compounds,
- Mercury (methyl mercury chloride, mercuric sulfide),
- Tin, organic compounds,
- Germanium (germanium dioxide).

Several studies on long-term lead-exposed monkeys and epidemiological studies on lead-exposed workers and children whose blood lead levels have been related to audiological findings, suggest that lead has an ototoxic effect caused by a neurotoxic mechanism (Araki et al., 1992; ATSDR, 2005; Bleecker et al., 2003; Counter & Buchanan, 2002; Discalzi et al., 1992, 1993; Farahat et al., 1997; Forst, Freels & Persky, 1997; Hirata & Kosaka, 1993; Holdstein et al., 1986; Murata et al., 1993; Osman et al., 1999; Schwartz & Otto, 1987, 1991; Wu et al., 2000). There are a few studies which do not confirm the effect of this metal on hearing (ATSDR, 2005; Counter et al., 1997a, b). However, given the current evidence from human studies, we recommend treating lead as an ototoxic agent.

Mercury compounds have been shown to induce hearing-damaging effects in laboratory animals (methyl mercury chloride, mercuric sulfide) and in human beings (organic mercury poisoning) (Chuu, Hsu & Lin-Shiau, 2001; Kurland, Faro & Siedler, 1960; Musiek & Hanlon, 1999; Rice & Gilbert, 1992; Rice, 1998; Wassick & Yonowitz, 1985).

Trimethyltin and triethyltin have been found to induce hearing impairments in rats and guinea pigs (Clerici, Ross & Fechter, 1991; Eastman, Young & Fechter, 1987; Fechter & Carlisle, 1990; Fechter, Young & Nuttall, 1986; Young & Fechter, 1986). Dose-related hearing impairment has been demonstrated in rats that have been given a single subcutaneous injection of 2, 4 or 6 mg/kg of trimethyltin chloride (Young and Fechter, 1986). In guinea pigs, an ototoxic effect has been observed after subcutaneous injection of 2 mg/kg of trimethyltin chloride and 12 or 24 mg/kg of triethyltin bromide (Clerici, Ross & Fechter, 1991). In guinea pigs treated with trimethyltin, outer hair cell loss and vascular changes (larger blood vessel diameter, atrophy) have been ascertained histopathologically in the stria vascularis (Fechter & Carlisle, 1990).

An acute limbic-cerebellar syndrome, which included inter alia hearing impairment and involuntary eye movements (nystagmus), was observed in six industrial workers who had inhaled trimethyltin. The severity of the symptoms paralleled maximal urinary organotin levels (Besser et al., 1987).

Rats and guinea pigs exposed to germanium dioxide by oral administration (100 mg/kg/day for 4 weeks and 0.5% in food for 2 months respectively) developed hearing impairments due to degeneration of the stria vascularis and the cochlear supporting cells (Yamasoba et al., 2006) and also showed alterations of brainstem transmissions (Lin, Chen & Chen, 2009).

4.2.2. Compounds with “fair evidence” of ototoxicity (suspected ototoxic substances)

▪ *Metals and metalloids*

- Cadmium (cadmium chloride)
- Arsenic

Rats exposed to drinking water containing 5 and 15 ppm cadmium chloride ($CdCl_2$) for 30 days have shown cadmium-induced signs of hearing impairment at a concentration of 5 ppm $CdCl_2$. Findings suggest that the cochlea is the main target for cadmium toxicity in the auditory system (Ozcaglar et al., 2001).

Hearing impairment has been observed in children living in an area heavily contaminated with arsenic. Analysis of the hair, blood and urine of children in the arsenic-polluted area revealed elevated arsenic content in these specimens (Bencko & Symon, 1977a, b; Bencko et al., 1977). Animal studies of sodium arsenilate (atoxyl) and its acetylated derivative (arsacetin) have shown histopathological changes in the organ of Corti and the stria vascularis (Anniko, 1976; Miller, 1985).

▪ *Bromates (sodium bromate, potassium bromate)*

Until now, no study has fully investigated the effects of bromates on humans or animals after low-dose long-term exposure. The ingestion of high-dose potassium bromate or sodium bromate has been shown to rapidly induce severe to profound permanent auditory impairments in humans (Gradus et al., 1984; Kamata et al., 1983; Matsumoto, Morizonom & Paparellam, 1980; for review, see Campbell, 2006). However, in other bromate-poisoning case reports, “no apparent hearing loss” was reported (Lichtenberg, 1989; Lue, Johnson & Edwards, 1988; Warshaw et al., 1985). Some guinea pig studies, show that the bromate-induced ototoxicity may be the result of stria vascularis, Reissner’s membrane and Corti’s organ cell impairments (Jahnke 1975; Kamata et al., 1983; Muratsuka, Ueda & Konishi., 1989; Takahashi et al., 1980). Due to the high doses applied in these experiments, any extrapolation of the results from animal studies to humans should be undertaken with caution. The lowest actual dose that causes ototoxicity has not been established, particularly for long-term low dose exposure. Currently no data exist on whether long-term low dose bromate exposure is actually ototoxic. Although if such a connection exists, it could go undetected due to the high rate of idiopathic (arising spontaneously or from an obscure or unknown cause) hearing impairment in the general public (Campbell, 2006).

▪ *Tobacco smoke*

There is an accumulating body of epidemiological research suggesting a positive association between smoking and hearing impairment (Barone et al., 1987; Cruickshanks et al., 1998; Ferrite & Santana, 2000; Mizoue, Miyamoto & Shimizu, 2003; Nakanishi et al., 2000; Nomura, Nakao & Morimoto, 2005; Nomura, Nakao & Yano, 2005; Palmer et al., 2004; Stanbury, Rafferty & Rosenman et al., 2008; Toppila et al., 2000, 2001; Wild, Brewster & Banerjee, 2006). A few studies, however, have not found any association between smoking and hearing impairment, such as Karlsmose et al. (2000) in Denmark. Starck, Toppila & Pyykkö (1999) suggested that smoking alone is not a risk factor of hearing impairment but can be in combination with other factors such as elevated blood pressure, use of painkillers or high cholesterol levels.

A disturbance in the blood flow and a reduction in oxygen supply to the cochlea have been proposed as the mechanisms on which this may be based (Palmer et al., 2004). It should also be mentioned that tobacco smoke contains hydrogen cyanide, an asphyxiant mentioned above (4.2.1, see also AGS, 2002).

▪ *Halogenated hydrocarbons*

- Polychlorinated biphenyls
- Tetrabromobisphenol A
- Hexabromocyclododecane
- Hexachlorobenzene

Rats that had been exposed during their early development (prenatally and during lactation via milk of their mothers) to polychlorinated biphenyls (PCB) were found to have light to moderate loss of outer auditory hair cells accompanied by elevated auditory thresholds (Crofton et al., 2000a, 2000b; Crofton & Rice, 1999; Goldey et al., 1995; Lasky et al., 2002; Powers et al., 2006).

Animal data suggest that halogenated hydrocarbon-induced hearing impairments are the sequelae of thyroid gland disorders caused by some of these substances (Goldey et al., 1995; Goldey & Crofton, 1998; Zoeller, 2005). In addition, Powers et al. (2006) proposed a direct adverse effect of poly-chlorinated biphenyls on the outer hair cell function.

Results of rat studies indicate that tetrabromobisphenol A and hexabromocyclododecane may elicit a disturbance in the processing of auditory information in the auditory system. The outcome pattern of audiometric tests suggests a predominant inner ear effect of hexabromocyclododecane, while tetrabromobisphenol A has general neural effects besides inner ear effects (Lilienthal, 2006; Lilienthal et al., 2008).

Results presented by Hadjab et al. (2004) suggest the ototoxicity of hexachlorobenzene in rats.

4.2.3. Compounds with "poor evidence" of ototoxicity (questionably ototoxic substances)

▪ *Insecticides*

- Pyrethroids
- Organophosphorous compounds

Reischl, van Gelder & Karam (1975) conclude from a small study that the insecticide parathion caused hearing impairment in squirrel monkeys.

Findings of Teixeira et al. (2002, 2003) among 98 Brazilian workers exposed to insecticides and 54 non-exposed workers indicated an association between the exposure to organophosphates and pyrethroids and damage to the central auditory nervous system and peripheral sensorineural hearing impairment. Crawford et al. (2008) also found that self-reported hearing impairments among licensed pesticide applicators could be associated with pesticide and notably organophosphate exposure.

By contrast, Ernest et al. (1995) failed to draw an association between hearing impairment and organophosphate exposure in insecticide-manufacturing workers. In fact, this relationship is difficult to ascertain because of a high number of confounding factors such as tractors and other farm machines (grinders, animal feeding equipment, power tools, chain saws, etc) which are major sources of noise, organic solvent and/or metal exposure or lifetime habits (cigarette and alcohol consumption).

▪ *Alkylic compounds*

- n-Heptane
- Butyl nitrite
- 4-tert-Butyltoluene

Concerning n-heptane, only one study has been identified in which hearing impairment was observed after the extremely high exposure to 4000 ppm of the compound, 6 h/d for 28 d (Simonson & Lund, 1995).

Rats exposed to butyl nitrite were found to have a loss of auditory sensitivity at 10 and 40 kHz tones. The data suggest that auditory function in the middle of the rats' auditory range, 10 kHz, was disrupted for a longer period than was high-frequency (40 kHz) auditory function. A disturbance of the cochlear oxygen supply was discussed as a possible cause of hearing impairment by butyl nitrite (Fechter et al., 1989).

4-tert-butyltoluene has been reported to affect auditory evoked potentials in rats (Lam et al., 2000; Lund & Simonsen, 1993).

▪ *Manganese*

In a small case study several decades ago, when 20 workers presenting symptoms of manganese intoxication were examined, a decrease in hearing ability and vestibular function was described, as well as the clinical symptoms of general poisoning. The same author further studied a group of workers exposed chronically to manganese in a battery factory. Workers with hearing impairment related to manganese exposure exhibited audiograms that show both low and high-frequency

sensorineural hearing impairment, with better thresholds in the middle-frequency range (Nikolov, 1974). We are not aware of more recent studies that independently confirm these results.

4.3. Use of ototoxic chemicals in industry

According to the Fourth European Working Conditions Survey (Parent-Thirion et al., 2007), the sectors with high exposure to noise and chemicals are “manufacture and mining”, “construction”, “electricity”, “gas and water supply” and “agriculture”.

Trends in chemical exposure have remained within a narrow range across the four surveys carried out by the EU Foundation since 1990. However exposure to noise has increased since 2000.

In 2001 hearing loss accounted for about 13% of all recognised occupational diseases (ODs) in Europe and was among the ten most common ODs in the 12 member states that participated in the first EUROSTAT statistical assessment EODS (EUROSTAT, 2004). Even if it is difficult to compare the absolute rates between the Member States due to certain variations in criteria for hearing impairment recognition, the data show that the highest incidence rate in nearly all of the national systems are in the same sectors: mainly manufacture (51% of the cases at EU-level, and especially the manufacture of metal products, wood products and transport equipment) and construction (17%). The same source quantifies neurological diseases linked to chemicals at 2%.

The EUROSTAT survey did not focus on hearing loss caused by ototoxic chemicals. But these data clearly indicate that the sectors with the highest prevalence of noise and chemical exposure are also the sectors with higher recognised occupational hearing impairment.

Examples of the major uses and sources of exposure to chemicals are described in Table 2. This table makes no claim of completeness. Nevertheless, it is obvious that ototoxic chemicals can be found in a wide range of industrial sectors. At several workplaces, co-exposure to two or more ototoxic substances may occur.

Table 2: Major uses/sources of exposure to ototoxic chemicals

CHEMICAL AGENT	MAJOR USES
Toluene	Production of benzoic acid, benzaldehyde, explosives, dyes, and many other organic compounds; solvent for paints, lacquers, gums, resins; extracting agent; petrol and naphtha constituent; additive; fabric and paper coating, artificial leather and detergent manufacture. Toluene is often found together with other solvents.
Ethylbenzene	Almost exclusively used for the production of styrene. Only a small proportion is used as a solvent.
n-Propylbenzene	Textile dying, solvent for cellulose acetate.
Styrene	Manufacture of plastics, rubber articles, glass fibres; synthetic rubber; insulators; used as a chemical intermediate, particularly in the resin and plastics production, component in agricultural products and stabilising agent.
Methylstyrene	Manufacture of modified polyester and alkyd resins. Low-molecular polymers are viscose liquids that are used as softener in polymers, paints and waxes.
Trichloroethylene	Solvent for a variety of organic materials. Trichloroethylene is a cleaning and degreasing agent and a means of extraction.

CHEMICAL AGENT	MAJOR USES
p-Xylene	Manufacture of resins, paints, varnishes, general solvent for adhesives; in aviation kerosene; protective coatings; synthesis of organic chemicals; solvent (e.g. for paints, coatings, adhesives and rubber); used in production of quartz crystal oscillators, perfumes, insect repellents, epoxy resins, pharmaceuticals, and in the leather industry. Used as a solvent in phenoxyalkanoic herbicides.
n-Hexane	Used as a cleaning agent in textile, furniture, and leather industries; laboratory reagent; component of many products associated with the petroleum and petrol industries; solvent, especially for vegetable oils; low-temperature thermometers; calibration; polymerisation reaction medium; paint diluent; alcohol denaturant. Used as reaction medium in manufacture of polyolefins, elastomers, pharmaceuticals and as a component of numerous formulated products.
n-Heptane	Used as a solvent in laboratories and for quick-drying glossy paints and glues.
Carbon disulfide	Manufacture of rayon, soil disinfectants, electronic vacuum tubes and carbon tetrachloride. Used as solvent for lipids, sulfur, rubber, phosphorus, oils, resins and waxes.
Carbon monoxide	Component of exhaust fumes emerging from incomplete combustion processes, e.g. in motor vehicles or poorly ventilated stoves and furnaces, acetylene welding or in enclosed areas (mines, tunnels).
Halogenated hydrocarbons	Intermediate product for the synthesis of organic compounds. Moreover they are used as solvents, anaesthetics, fire-extinguishing agents, refrigerants and propellants.
Nitriles	Used for the preparative synthesis of carboxylic acids. Of commercial importance are acetonitrile as a solvent, benzonitrile as an initial compound for melamine resins and acrylonitrile as a monomer for polyacrylonitrile.
Cyanides	Used as an intermediate product in the organic synthesis of carboxylic acids, pharmaceuticals, dyes and pesticides. Relatively large quantities are also required for the surface treatment of metals, galvanising and the cyanide leaching process.
Lead	Manufacture of lead-acid batteries; ship breaking; manufacture of paint; also in petrol and plastic manufacture, may emerge during car radiator repair; welding; plumbing; smelting, refining and mining.
Mercury	Used in the chloralkali industry. Mercury compounds may be used in batteries (mercuric oxide), pigments, catalysts, explosives (mercury fulminate), laboratory-based research, and in some pharmaceutical applications.
Manganese	Manufacture of steel alloys, dry-cell batteries, electrical coils, ceramics, matches, glass, dyes, in fertilizers, welding rods, as oxidizing agents, and as animal food additives.
Tin, organic compounds	Tri-n-alkyltins are phytotoxic and can be powerful bactericides and fungicides.
Arsenic	Production of pesticides, smelters, semiconductors, antifouling paints, electroplating industry and pigments.

CHEMICAL AGENT	MAJOR USES
Cadmium	Protective plating on steel, stabiliser for polyvinyl chloride, pigments in plastics and glass, electrode material and component of various alloys.
Germanium (germanium dioxide)	Used as a semi-conductor in transistors, in light-emitting diodes, solar cells, thermo-generators, glass and alloys.
Bromates	Used as powerful oxidants.
Organophosphorous compounds	Used as insecticides in agriculture.

5. Combined effects

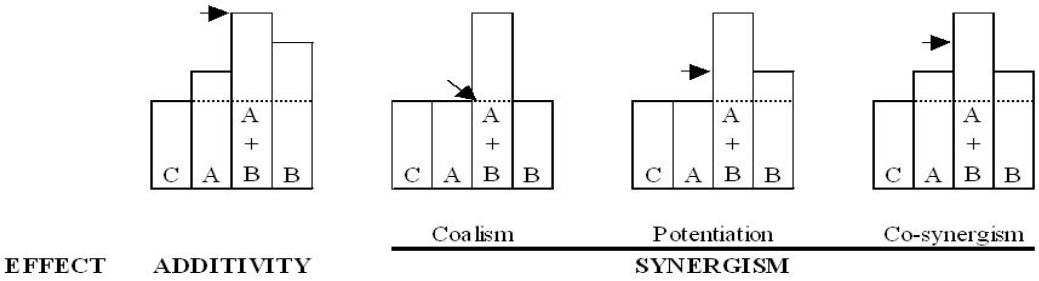
Several work-related ototoxic substances like solvents, heavy metals, asphyxiants and certain drugs are known to be ototoxic by themselves. Investigations which deal with combined exposures to different ototoxic substances or simultaneous exposure to ototoxic substances and noise have shown adverse interactive effects on hearing. These interactive effects could be additive or synergistic (Figure 6). According to Calabrese (1991) and Greco et al. (1992), the interactive effects can be defined as:

- an additive effect, which would be the predicted sum of the effects of single exposures,
- a synergistic effect, which would have a greater amplitude than that obtained by the predicted sum of the single effects.

Synergism is a more complex concept, which can be subdivided in several classes (Figure 6):

- coalism, in which none of the agents is effective individually,
- co-synergism, in which both separate agents are effective,
- potentiation, in which only one agent is effective individually.

Figure 6: Illustration of different outcomes after exposures to agents A and B. C = control (unexposed) group. Arrows indicate predicted effects. Dotted lines indicate control values (from Nylén, 1994).



5.1. Effects of combined exposure to various (ototoxic) substances

Toxic interactions of loop diuretics and other known ototoxic drugs have been well documented, and particularly the interaction involving aminoglycoside antibiotics, both in human and animal studies (Miller, 1985). The aminoglycosides primarily damage auditory hair cells, whereas loop diuretics damage the stria vascularis. Thus, combined treatment results in two sites of injury within the cochlea. It has to be emphasised that the hair cells are dependent on the stria vascularis for maintaining normal inner ear fluid composition. Moreover, damage to the stria vascularis may result in increased entry of the aminoglycosides into the inner ear fluid (Walker, Fazekas-May & Bowen, 1990).

Ethacrynic acid is also known to interact with cisplatin, a known ototoxic antineoplastic drug (Komune & Snow, 1981).

With regard to industrial chemicals, ototoxicity potentiation caused by ethylbenzene has been observed in rats exposed to mixed xylene isomers. The enhanced ototoxicity of ethylbenzene and p-xylene observed in simultaneous exposure to ethylbenzene and mixed xylenes was attributed to toxicokinetic interactions between the test substances (Gagnaire et al., 2007b).

An additive ototoxic effect has been observed in rats exposed to mixtures of styrene and trichloroethylene (Rebert et al., 1993).

Results of a rat study indicate that the ototoxic effect of cadmium may be potentiated by the diuretic drug furosemide (Whitworth, Hudson & Rybak, 1999).

In rats, acetyl salicylic acid was found to enhance the auditory sensitivity loss induced by toluene (Johnson, 1993).

Ethanol, probably as a result of competitive metabolic inhibition, is capable under certain circumstances of increasing the concentrations of styrene, toluene and p-xylene in the blood and hence the ototoxicity of these solvents (Campo & Lataye, 2000; Cerny et al., 1990; Coccini et al., 1998; NIOSH, 1987, Wilson et al., 1983). As a result, the hearing impairment induced by a simultaneous exposure to both ethanol and the aforementioned compounds may be larger than that induced by exposure to the aromatic solvents alone.

5.2. Combined effects with noise

5.2.1. Pharmaceuticals

Some studies indicate that the administration of ototoxic drugs such as aminoglycosides produces increased susceptibility to noise-induced damage (Brown et al., 1981; Falk et al., 1972; Mills & Going, 1982).

Salicylate-induced temporary threshold shifts may exacerbate temporary noise effects due to the reduced comprehension of speech and difficulty to detect acoustic alarms in noisy environments (Young and Wilson, 1982). So far, it is not known whether salicylates in combination with environmental noise would promote permanent noise-induced hearing loss (Pyykkö et al., 1989).

For antitumour drugs, an exacerbation of cisplatin ototoxicity was observed in chinchilla and guinea pigs with concomitant moderate to high levels of noise exposure (Boettcher et al., 1987; Gratton et al., 1990; Laurell, 1992).

5.2.2. Solvents

Experiments with rats have shown that combined exposure to noise and solvents such as:

- toluene (Brandt-Lassen, Lund & Jepsen, 2000; Johnson et al., 1988; Lataye & Campo, 1997; Lund & Kristiansen, 2008),
- styrene (Lataye, Campo & Loquet, 2000; Lataye et al., 2005; Mäkitie et al., 2003),
- ethylbenzene (Cappaert et al., 2001),
- trichloroethylene (Muijser, Lammers & Kullig, 2000).

induced synergistic adverse effects on hearing. High levels of noise and high concentrations of solvents were used in most of these investigations. Because of these special conditions, these data cannot be easily extrapolated to occupational exposure conditions (Cary et al., 1997). However, Lataye et al. (2005) found interactive effects of noise at a relatively low intensity level of 85 dB and a styrene exposure concentration of 400 ppm.

Although the cochlea suffers damage particularly during co-exposure, recent studies have reported that solvents reduce the protective role played by the middle-ear acoustic reflex, an involuntary muscle contraction that normally occurs in response to high-intensity sound stimuli. A disturbance of this reflex would allow the penetration of a hazardous higher acoustic energy into the inner ear (Campo, Maguin & Lataye, 2007; Lataye, Maguin & Campo, 2007; Maguin, Campo & Parietti-Winkler, 2009).

A number of epidemiological studies have investigated the relationship between hearing impairments and co-exposure to both noise and industrial solvents (Chang et al., 2003, 2006; De Barba et al., 2005; Johnson et al., 2006; Kim et al., 2005; Morata, 1989; Morata et al., 1993, 2002; Morioka et al., 2000; Prasher et al., 2005; Sliwinska-Kowalska et al., 2003; 2005). Due to confounding factors, straightforward conclusions could not be easily drawn. However, the likely additive or synergistic

ototoxic effects due to combined exposure to noise and solvents cannot be denied (Lawton, Hoffmann & Triebig, 2006; Hoet & Lison, 2008). Given the difficulty in (1) extrapolating the animal findings and (2) analysing the data obtained in humans, regulators have to pay attention to both experimental and epidemiological studies.

A recent longitudinal study (Schäper et al. 2003; Schäper, Seeber & van Thriel, 2008) on the relationship between hearing impairment measured by pure tone audiometry and occupational exposure to toluene and noise has not found ototoxic effects in workers exposed to a concentration of toluene lower than 50ppm. The observed hearing loss was associated only with noise intensity. However, the use of hearing protection was not taken into account in the conclusions relative to the potential interaction between noise and toluene on hearing.

Overall, in combined exposure to noise and organic solvents, interactive effects may be observed depending on the parameters of noise (intensity, impulsiveness) and the solvent exposure concentrations. In case of concomitant exposures, solvents can exacerbate noise-induced impairments even though the noise intensity is below the permissible limit value.

5.2.3. Asphyxiants

In laboratory animal models

- carbon monoxide and
- cyanides

have been found to potentiate permanent noise-induced hearing loss (Chen & Fechter, 1999; Chen, McWilliams & Fechter, 1999; Fechter, Chen & Johnson, 2002 Fechter, Cheng & Rao, 2000; Fechter et al., 2000; Fechter, Young & Carlisle, 1988; Rao & Fechter, 2000; Young et al., 1987). Combined exposure can also induce threshold shifts in some cases in which both the noise and the carbon monoxide alone did not cause threshold shifts (case of coalism). It was also observed that the hearing loss induced by noise alone gradually recovered (partially), but the hearing loss caused by the combined exposure did not. The potentiation may be due to the reduction of the cell's ability to repair noise-induced damage by carbon monoxide (Chen, McWilliams & Fechter, 1999).

In a short abstract, Lacerda, Leroux & Gagn (2005) reported results of a study in which the hearing thresholds of employees in noisy working environments with and without combined carbon monoxide exposure were compared. The analysis was based on 9396 audiograms collected by the Quebec National Public Health Institute between 1983 and 1996. The results show significantly higher hearing thresholds at high frequencies (3, 4 and 6 kHz) for the group exposed to carbon monoxide, with more pronounced effects being observed with increasing length of exposure (15 to 20 years of exposure). The authors concluded a potentiation effect of noise-induced hearing impairment by carbon monoxide in humans.

5.2.4. Nitriles

After subcutaneous administration of acrylonitrile, rats showed a significant potentiation of noise-induced hearing impairment (Fechter et al., 2003; Fechter, Gearhart & Shirwany, 2004). Under test conditions in which individually neither acrylonitrile nor noise exposures caused any permanent hearing or hair cell loss, combined exposure caused permanent hearing impairment and significant loss of outer auditory hair cells (case of coalism; Pouyatos, Gearhart & Fechter, 2005).

Thus, hearing loss may occur at lower levels of noise if there is simultaneous exposure to acrylonitrile. Pouyatos, Gearhart & Fechter (2005) put forward the hypothesis that acrylonitrile increases the risk of noise-induced oxidative damage to the inner ear by impairing cellular antioxidative defence mechanisms.

5.2.5. Manganese

Nikolov (1974) reported that the potential ototoxicity of manganese may be exacerbated by exposure to noise and that workers exposed to both manganese and noise seem to have accelerated hearing impairment compared to those exposed to manganese alone.

5.2.6. Tobacco smoke

Results of epidemiological investigations indicate that smokers may have an increased risk of noise-induced hearing impairment (Wild et al., 2005; Barone et al., 1987). In some studies the combined effects of smoking and exposure to noise on hearing were estimated to be additive (Mizoue, Miyamoto & Shimizu, 2003; Palmer et al., 2004; Uchida et al., 2005). The additional risks were small compared to those of long-term noise exposure, and the combination of effects was more consistent with an additive than a multiplicative interaction.

In contrast, based on results of a cross-sectional study, a synergistic effect of smoking, noise exposure and age on hearing loss has been reported (Ferrite & Santana, 2005). In another study an insignificant statistical interaction of occupational noise exposure with the association between smoking and hearing loss was found (Nomura, Nakao & Yano, 2005).

6. Present policies

6.1. International Organisations

The programme of the World Health Organisation (WHO) on noise and health reviews the main health effects of noise from a dose-effect perspective (WHO, 2007). It identifies the needs of specific vulnerable groups and mentions the importance of "complex interactions". In the WHO's Special Report "Occupational exposure to noise: evaluation, prevention and control" (Goelzer, Hansen & Sehrndt, 2001), the combined exposure to noise and other factors such as solvents, vibrations or metal dust are cited and it is suggested that more stringent criteria than those specified as standard in the document should be applied.

The International Labour Organisation (ILO) has issued the following labour standards related to noise and chemicals: C148 Working Environment (Air Pollution, Noise and Vibration) Convention, 1977, and C170 Chemicals Convention, 1990, and the related Recommendations No. 156 and 177. None of them take into account combined exposure to noise and chemicals.

In 1980, to ensure efficient chemical management, the International Programme on Chemical Safety (ICPS) was launched as a joint programme of three cooperating entities, namely the International Labour Organisation, the World Health Organisation and the United Nations Environment Programme. The International Chemical Safety Cards (ICSCs) were developed on this basis. They consist of a series of standard sentences summarising health and safety information, collected, verified and peer-reviewed by internationally recognised scientists. The cards have no legal status and may not reflect in all cases the detailed requirements included in national legislation. Ototoxic properties are acknowledged on the ICSCs for toluene, xylene and potassium bromate; for toluene and xylene under the conditions of co-exposure to noise. For other ototoxic chemicals including styrene and ethylbenzene there is no indication of ototoxicity on the corresponding ICSCs.

6.2. EU policy

Health and safety at work is one of the most vigorous areas of EU social policy. EU Directives provide a common framework for EU member States and are an effective device for establishing basic rules at workplaces. The protection of workers' health from exposure to chemicals and noise is treated particularly in:

- Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work (14th individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC),
- Directive 2003/10/EC on the minimum health and safety requirements regarding the exposure of workers to the risks arising from physical agents (noise) (17th individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC).

The issue of occupational hearing loss is monitored mainly by specific prevention programmes that are mainly shaped by Directive 2003/10/EC and its transposition to the national legislation, by available guidelines and effective practices and, at last but not least, company policies.

In addition to occupational health and safety issues the EU chemical agent legislation regulates the internal market (http://www.echa.europa.eu). Directive 98/24/EC (Chemical Agents Directive) brings a coherent approach to the provisions of the Framework Directive, while the REACH Regulation concerns the registration, evaluation, authorisation and restriction of chemicals. One of the main differences between the Chemicals Directive and REACH is in the risk assessment area: REACH limits risk assessment to tonnages >10 tonnes/year while the Chemical Directive demands risk assessments for all chemicals used at the workplace.

The EU Noise Directive 2003/10/EC lays down the minimum requirements for the protection of workers from risks to their health and safety due to exposure to noise. Art. 4 of the directive envisages the obligation of the employer to carry out the risk assessment and lists a number of aspects for consideration in that regard including the requirement to prevent or reduce risks not only from exposure to noise at work but also to the combined exposure to noise and occupational ototoxic compounds.

In the Noise Directive, the combined exposure to noise and chemicals is mentioned in one discrete clause (Article 4 clause 6d):

“the employer shall give particular attention, when carrying out the risk assessment, to the following:

[…] as far as technically achievable, any effects on workers' health and safety resulting from interactions between noise and work-related ototoxic substances, and between noise and vibrations”.

It is noteworthy that in the Noise Directive the corresponding control measure recommendations are confined to reducing noise exposure.

The 5th framework programme of the European Community for research, technological development and demonstration activities (1998 - 2002) provided two projects dealing with the interaction of industrial chemicals and noise on hearing and balance within the key Action 4 – Environment and Health. In work package WP3 of the project “Noise Pollution Health Effects Reduction (NOPHER)”, carried out between 2001 and 2003, approaches were made to establish unified protocols and initiate field studies across Europe to determine the extent of auditory damage from exposure to industrial chemicals with and without noise (European Commission, 2003; Prasher, 2000). A large study on noise and industrial chemicals entitled “Interaction Effects on Hearing and Balance (NoiseChem)” was conducted by partners in Sweden, Finland, France, Denmark, the United Kingdom and Poland with expert guidance from U.S. partners in the period 2001-2004. One research group endeavoured to determine mechanisms of ototoxic damage due to the interaction of noise and chemicals by means of laboratory investigations with animals, while a second group examined the effects of organic solvents, solvent mixtures and noise on human audio-vestibular systems through epidemiological surveys in factories. Findings from this study were presented in a final report (Prasher et al., 2004) but have not yet led to consequences in European legislation in this field.

6.3. Policies in EU Member States: some examples

In France, scientists from the Institut National de Recherche et de Sécurité (INRS) proposed lowering the occupational exposure limit (permissible time-weighted average or VME8h) for styrene from 50 to 30 ppm in addition to the compulsory use of hearing protectors for 8-hour noise exposure to 80 dB(A) (Campo and Maguin, 2006). The rationale for this initiative can be briefly explained as follows:

- In a dose-response protocol with “active” rats, a 300 ppm exposure to styrene (6 hours/day, 5 days/week, 4 weeks) produced a clear cochleotoxic effect on the third row of outer hair cells. This dose (300 ppm) could be regarded as the experimental lowest observed adverse effect level (LOAEL) and was used as a “reference dose” or “point of departure” for deriving an occupational exposure limit. A safety factor of 10 was then applied to take account of uncertainties and to extrapolate a not adverse effect level from the LOAEL. It is expected that this factor will not exaggerate workers’ protection. As 300 divided by 10 equals to 30, a decrease in the existing French VME8h for styrene (50 ppm) was recommended to ensure a higher level of protection for human hearing. According to INRS, a similar strategy could be used for other suspected chemicals.
- In the case of co-exposure to noise and solvent, not only does the occupational exposure limit for styrene have to be observed, but also, according to regulations in force, hearing protectors are required if the sound pressure level exceeds the so-called upper exposure action value of 85 dB(A). Taking into consideration the risk of synergies, however, INRS recommends for precautionary reasons stipulating the use of hearing protectors at the lower exposure action value, i.e. 80 dB(A).

This pilot approach aimed to encourage a more general and consensual debate and explicitly leaves room for constructive suggestions and alternatives.

In 2006, Germany held a large conference on ototoxicity and noise in Hennef. During the panel discussion, the participants agreed on the following conclusions regarding the current workplace situation (Milde, Ponto & Wellhäußer, 2006):

- If the current limit values (which are generally derived from toxicological endpoints other than ototoxicity) for industrial chemicals with proven or suspected ototoxic effects are adhered to, the probability of significant hearing loss is low.

- There can be a higher risk in activities involving ototoxic industrial chemicals if the limit values are exceeded (e.g. when processing styrene).
- Noise is the highest risk factor for hearing damage. Hence, measures to combat noise-induced hearing loss continue to have top priority.

In keeping with the precautionary principle of the EU Commission which calls for an adequate level of protection for employees even when the scientific data available are insufficient, ambiguous or unreliable, the following recommendations are being made by the Noise Working Group and the Hazardous Substances Working Group, of the German Social Accident Insurance (DGUV) Committee for Occupational Medicine:

- Risk-management measures aimed at decreasing exposure to ototoxic industrial chemicals (substitution, reduction of emissions, changes in processing and production techniques, etc.) should be supported.
- Public risk communication, including all points of contact (manufacturers, users, company doctors and safety specialists), should be promoted.
- The issue should be incorporated into occupational health-screening activities (educating and advising employers and employees; it should be considered when assessing the patient's history).
- Scientific approaches (e.g. longitudinal studies) aimed at characterising the risk potential of ototoxic industrial chemicals and their effect when combined with noise should be supported for the purposes of hazard assessment.
- Adequate tools for early diagnosis should be developed.
- The ototoxicity endpoint should be taken into account when deriving occupational exposure limits.

These conclusions were endorsed at the Annual Conference of the German Association of Occupational Environmental Medicine in 2007 (Milde, 2007).

The German position on the current workplace situation is that heightened risk may in particular arise during activities with ototoxic agents if the current occupational exposure limit values are exceeded. The BGIA MEGA exposure database on hazardous substances (Gabriel, 2006; Van Gelder, 2006) is a database containing measured values from German workplaces. By means of this database, industrial sectors and workplaces can be identified in which ototoxic substance concentrations are above the limit value. The results are about to be published in the "BGIA-Handbuch" to encourage further action.

By means of the BGIA MEGA exposure database on hazardous substances and the BGIA MELA exposure database on noise it is planned to spot sectors of industry and working areas in which hazard substances and noise are at particularly high levels. This approach is feasible since both databases use the same coding for industrial sectors and working areas. Some examples are given in the annex 1.

As a guide for the enforcement of the Spanish transposition of the Noise Directive, the National Institute for Occupational Safety and Hygiene (INSHT) has published guidance in Spain on how to deal with the combined exposure of noise and ototoxicants. In brief, its main points are to treat workers exposed to noise and ototoxic substances as a vulnerable group; to install an audiometric control independently of the level of noise exposure; to intensify medical surveillance; to add relevant audiological tests to audiometric control (otoacoustic emissions and high-frequency audiometry are suggested); to treat as vulnerable workers (temporarily or permanently) workers exposed to ototoxic drugs and therefore ought to use suitable personal protective equipment while being exposed (INSHT, webpage).

6.4. Policies in other countries

In 1996, the U.S. National Institute for Occupational Safety and Health (NIOSH) developed the National Occupational Research Agenda (NORA), a research framework to encourage innovative

research and improved workplace practices. 21 topics were identified as priority areas for OSH research. “Hearing Loss” and “Mixed Exposures” are two of the priority topics in NORA that are addressed by the NIOSH Hearing Loss Research (HLR) programme (NIOSH, webpage). Currently the programme supports strong currents of new research in ototoxic chemical exposure and their synergistic and additive effects on noise exposure, engineering control of noise, and research on the efficacy of new technologies in hearing protection devices. As early as 1988, the HLR programme identified the need to “determine […] the degree to which noise interacts with other agents […] to affect hearing.” In the research goal 4.6 of the HLR programme “Prevent hearing loss from exposure to ototoxic chemicals alone or in combination with noise”, the following sub-goals were adopted:

- identify specific ototoxic chemicals or classes of chemicals of concern and characterise the risk;
- bring this risk to the attention of workers, public health professionals, and policy makers; and
- develop specific recommendations.

To address those goals, the HLR programme established partnerships with several universities and national and international health organisations. The HLR programme is mirrored in statements and safety measures of external groups:

- In the noise section of its Threshold Limited Values and Biological Exposure Indices (TLVs® and BEIs®), the American Conference of Industrial Governmental Hygienists (ACGIH, 2009) has inserted the following note: “In settings where there may be exposures to noise and to carbon monoxide, lead, manganese, styrene, toluene, or xylene, periodic audiograms are advised and should be carefully reviewed.”
- Since 1998, the U.S. Army has required the inclusion of ototoxic chemical exposures in its hearing conservation programme, “particularly when in combination with marginal noise”. The U.S. Army Fact Sheet 51-002-0903 on Occupational Ototoxins and Hearing Loss states that since the exposure threshold for ototoxic effects is not known, audiometric monitoring is necessary to determine whether the substance affects the hearing of exposed workers. It includes recommendations for yearly audiograms for workers whose chemical exposure (disregarding the wearing of respiratory protection) equals 50% of the most stringent criteria for occupational exposure limits, regardless of the noise level.
- The evidence-based “Noise-induced Hearing Loss” statement of the American College of Occupational and Environmental Medicine (ACOEM) emphasises that “co-exposure to ototoxic agents, such as solvents, heavy metals and tobacco smoke, may act in synergy with noise to cause hearing loss”. The statement continues as follows: “However, the role of such cofactors – as well as the role of cardiovascular disease, diabetes, and neurodegenerative diseases – remains poorly understood. Individual susceptibility to the auditory effects of noise varies widely, but the biological basis for this also remains unclear” (ACOEM, 2003).

The latest information on NIOSH activities on workplace hearing are described in the NIOSH science blog (NIOSH, Science blog website, 2009).

The Australian-New Zealand Standard AS/NZS 1269.0 (Appendix C) includes information on ototoxic substances and recommends that for those exposed to "known or suspected ototoxic agents their noise exposure limits should be reduced as a precautionary measure" and requires hearing tests (Burgess & Williams, 2006).

7. Conclusions

▪ *Substances of concern*

Evidence of hearing impairment caused by chemicals at the workplace and combined effects of exposure to noise and ototoxic chemicals has emerged predominantly as a result of animal tests in which such associations have been demonstrated. These findings are supported to some extent by a number of epidemiological studies on workers employed in different industrial sectors. At this time, however, the exact magnitude of the problem under lower exposure conditions at today's workplaces in Europe is not yet clear.

Bearing this in mind, risk control should be based on the precautionary principle. The present report applies a weight-of-evidence based classification scheme for ototoxic chemicals. According to current knowledge, the following substances should be considered confirmed ototoxic agents and therefore be prioritised as regards risk reduction measures at occupational settings:

Substance class	Chemicals
Pharmaceuticals	Aminoglycosidic (e.g. streptomycin, gentamycin) and some other antibiotics (e.g. tetracyclines), loop diuretics (e.g. furosemide, ethacrynic acid) certain analgesics and antipyretics (salicylates, quinine, chloroquine) and certain antineoplastic agents (e.g. cisplatin, carboplatin, bleomycin).
Solvents	Carbon disulfide, n-hexane, toluene, p-xylene, ethylbenzene, n-propylbenzene, styrene and methylstyrenes, trichloroethylene.
Asphyxiants	Carbon monoxide, hydrogen cyanide and its salts.
Nitriles	3-Butenenitrile, cis-2-pentenenitrile, acrylonitrile, cis-crotononitrile, 3,3'-iminodipropionitrile.
Metals and compounds	Mercury compounds, germanium dioxide, organic tin compounds, lead.

Furthermore, cadmium and arsenic compounds, as well as halogenated hydrocarbons (polychlorinated biphenyls, tetrabromobisphenol A, hexabromocyclododecane and hexachloro-benzene), alkali bromates (at least high dose exposure), and tobacco smoke are strongly suspected of having ototoxic potential.

The relevance of the occasionally reported ototoxic properties of manganese, butyl nitrite, n-heptane, 4-tert-butyltoluene and certain insecticides (organophosphorous compounds, pyrethroids) at the workplace has to be substantiated or falsified by more adequate scientific studies.

The present ranking system identifies more ototoxic substances than an independent approach by the Canadian occupational health and safety research institute IRSST (Vyskocil et al., 2009), the latter classifying only lead and inorganic compounds, toluene, styrene and trichloroethylene as "ototoxic substances", and regarding n-hexane, ethylbenzene and xylene (all isomers!) as "possibly ototoxic". The IRSST literature review predominantly covers the period 1970 to 2005, although several more recent references are mentioned in the annex. The data were evaluated only for a limited range of exposure concentrations (e.g. up to 100 times the 8-hour time-weighted average exposure limit value in Quebec). Substances with a strong evidence of ototoxicity in animal studies for which no relevant human study was found were rated as "possibly ototoxic". Interactive effects of chemicals and noise were not taken into consideration. In contrast, the present EU report focuses on the *qualitative* properties of chemicals to induce ototoxic effects and decisively relies on animal studies when classifying the rate of evidence. In some cases, our rating was based on a broader data set than that of Vyscocil et al. (2009) and included adverse interactive effects with noise as well as structure-activity relationships.

▪ *Gaps in the research*

Unfortunately, the published data on the combined health effects of ototoxic substances and noise are rather limited. Moreover, there is evidence that hand-arm and total-body vibration induce hearing impairment and aggravate noise-induced hearing loss. The exact nature of hearing damage caused by vibration and the mechanism underlying the interactive effects of noise and vibration are presently being studied (Sutinen et al., 2007). Obviously, there is a lack of data concerning the health risks of combined exposures to ototoxic substances, noise and vibration.

In general, there is only scarce scientific knowledge and understanding of the risks of combined exposures, as research has traditionally focused on single factors. This is partly due to epistemological and practical problems. If in a bioassay all possible interactions of various impacts at different levels are to be studied in equal measure, the number of experimental groups rises exponentially with increasing numbers of applied agents. The interpretation of the results requires an elaborate statistical analysis.

However, the reality of concurrent or sequential exposure of humans to multiple chemical, physical, biological, psychological and socioeconomic stressors calls for substantial insight into the hygienic consequences of such complex impacts. Promising tools have been developed for overcoming some of the inherent problems when assessing the risks of combined exposure (Jonker et al., 2004). These tools include more efficient statistical designs, tiered approaches or the use of mechanistic models. Ideally, singular endpoints could be examined that are representative of a particular detrimental mechanism for which joint action or interaction is expected. Novel methods for rapidly elucidating modes of action and finding early molecular markers, e.g. the “-omics” technologies, should foster this effort.

With respect to individual ototoxic substances, further investigation is needed to assess workplace risks caused by those substances rated “suspected” or “questionably ototoxic” in this report and to identify additional substances with occupational relevance and ototoxic potential. There is a demand for the targeted identification and investigation of the most potent ototoxic agents, supported by an improved understanding of their action mode. The incrimination of diffuse chemical classes like “solvents” or “pesticides” seems to be inappropriate when specific protection and substitution measures at workplace level are required.

Most epidemiological studies on the ototoxicity of industrial chemicals – mainly focusing on occupational exposure to styrene, toluene, solvent mixtures and carbon disulfide and combined exposure to noise and solvents such as toluene, styrene, and ethylbenzene – have been cross-sectional studies. These studies are able to identify the problem but frequently fail to quantify it. One reason for this is the "healthy worker" phenomenon. Workers who are susceptible to the harmful agent are removed from the workforce through early retirement, unemployment or just by changing the job and are thus not properly recorded. Furthermore, chronic effects are related to currently measured exposures. The exposure concentrations measured at the time of the study, however, can in some cases be markedly lower than those ascertained in the past years. All in all, there is a lack of clear data on dose-response relationships and thresholds for ototoxic effects in humans.

To overcome this, well-designed longitudinal studies are needed to evaluate the impact of noise and work-related ototoxic substance exposure in humans. “Well-designed” means in this context that the social impacts and other confounders as well as all aspects of hearing impairment are included in the study. As an example, styrene may affect vision, balance and hearing.

Moreover, adequate epidemiological studies should identify early symptoms of hearing impairment with systems allowing the revealing of minor cochlear dysfunction as well as retrocochlear lesions throughout the signal transmission chain from the ear to higher auditory centres.

In most EU countries, hearing handicap testing is confined to hearing impairment instead of measuring a loss of communication skills. This is also true for the majority of relevant epidemiological studies. Although hearing impairment is simple to measure, this approach causes problems that have a strong bearing on combined exposure to noise and ototoxic chemicals because several organs may be affected. If only physiological changes are measured, there is a lack of information on the psycho-social consequences for everyday life and the impairment of communication skills may be highly underestimated. The correlation of pure tone audiometry (PTA), for instance, with subjective evaluation and handicap turns out to be rather poor (Barrenäs & Holgers, 2000).

All in all, the audiological control of workers exposed to noise, chemicals or both should go further than PTA or otoacustic emissions measurement in taking account of the main dimensions of hearing impairment. A combination of several tests and questionnaires is needed for early detection and proper evaluation of the total effects on workers' hearing and quality of life.

Essential for a risk assessment of ototoxic substances and noise is the identification of risk groups. Exposure databases and exploratory studies using anonymised and grouped health surveillance data could be helpful for the identification of high-risk industrial sectors and workplaces in which ototoxic substances and noise occur. They should be designed to comply with all aspects of the problem.

Given the difficulties of interpreting data from epidemiological studies, data obtained from animal models cannot be neglected and should serve as a basis for precautionary measures. They make it possible to assess the specific effect of several substances or factors studied in controlled and proper experimental conditions. Therefore, they contribute significantly to the determination of effect thresholds for humans.

With regard to animal tests, thought should be given to the fact that passive nocturnal species are usually employed. As the effects of noise and most ototoxic chemicals are dependent on the metabolic rate, animal research should use active animals in the evaluation of harmful effects or apply safety factors to establish threshold limit values.

▪ *Gaps in regulations*

In the EU, there is no common regulation that requires the monitoring of hearing for workers exposed to ototoxic chemicals without significant noise exposure. Neither are there European standards which contain explicit requirements relating to co-exposure to noise and ototoxic substances. The EU Noise Directive 2003/10/EC simply stipulates in Article 4.6.c that "any effects concerning the health and safety of workers belonging to particularly sensitive risk groups shall be taken into account in risk assessment". Since specific instructions are lacking and the knowledge of specific risk factors for hearing impairment, like tobacco smoking or consuming ototoxic drugs, is poor, compliance with and the effective implementation of this rule is questionable. Little is being done or even proposed within the various EU Member States to deal with the problem at a national level.

More frequent medical surveillance should be considered for workers co-exposed to noise and ototoxic substances, irrespective of the noise exposure level, and workers' health results should be recorded in order to detect early changes at individual and collective levels. The aim of health surveillance is to have a system which identifies early symptoms of hearing impairment. Otoacoustic emission measurements (in particular TEOAE, see chapter 2) could be a valuable complement to pure tone audiometry (PTA) recordings.

Ideally, an interview by an occupational doctor should take place with subsequent listing of potential ototoxic drugs consumed during a hospitalisation period before returning to work. Based on the precautionary principle, the use of individual hearing protectors from an exposure limit of 80 dB(A) in a complex occupational environment (noise plus chemical ototoxic substances) should be recommended. A special label for ototoxic substances may be considered.

Moreover, it is important not to neglect the importance of the education and motivation of the relevant stakeholders in hearing conservation programmes including exposure to chemicals.

In many cases the exposure to ototoxic chemicals may occur through dermal uptake, for which air-concentration-based occupational exposure limits provide no protection. In order to control the total body burden, biomonitoring is needed. Biological tolerance values, however, exist for only a small number of ototoxic chemicals. Moreover, these limit values are based on endpoints other than ototoxicity.

Occupational exposure limits are based on "critical effects". A critical effect is the adverse health effect that is detected at the lowest exposure level – regardless of its nature. Ototoxicity is not tested as a matter of routine. This endpoint, which in addition could occasionally be used as an early indicator of neurotoxicity, should be given higher priority when evaluating the toxicity of industrial chemicals and establishing occupational exposure limits.

Tests for ototoxicity therefore have to be standardised and incorporated into national and international guidelines. Relevant regulatory research should include bioassays applying minimum- and sub-effect concentrations of the individual stressors. Nevertheless, a deeper insight in the mode of action of ototoxic substances and their interaction with noise is an essential prerequisite for adequate risk management measures.

Even though the EU Regulation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) does not aim to modify the Chemical Agents Directive, REACH will necessarily provide more information on the physico-chemical, health and environmental properties of hazardous substances, improve labelling and safety data sheets, thus enabling employers to carry out an improved risk assessment as required by Directive 98/24/EC. Toxicological endpoints so far neglected should benefit from this policy, the more so because the Globally Harmonised System (GHS), recently adopted in the EU, has introduced in an innovative manner the matter of specific target organ toxicity. It is hoped that in this context the ototoxic effects of workplace substances can be addressed more systematically.

8. References

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9. GLOSSARY

Analgesic: drug used to relieve pain ("painkiller").

Antineoplastic agent: drug used to treat cancer.

Antipyretic: drug used to reduce fever.

Audiogram: graph showing hearing thresholds or hearing abilities of an individual for different acoustic signals (example: see Figure 4) resulting from ►audiometry. Common way of representing a person's hearing loss.

Audiometry: testing of hearing ability. The standard method is conventional pure tone audiometry (PTA), recording a person's hearing level measured with certain pure tones, mainly at frequencies of 250, 500, 1,000, 2,000, 3,000, 4,000, 6,000 and 8,000 ►Hz.

Auditory cortex: region in the outer ("cortical") portion of the brain where acoustic information is processed.

Basilar membrane: selective barrier separating two liquid-filled tubes that run along the coil of the ►cochlea, namely the "scala media" (cochlear duct) and the "scala tympani" (see Figure 2).

Chemotherapeutic agent: drug selectively toxic to the causative agent of a disease, such as malignant cells, viruses, bacteria, or other microorganisms.

Cochlea: snail-shell-like structure of the inner ear divided into three fluid-filled compartments (see Figure 2). Two are canals for the transmission of pressure. The third compartment is called "cochlear duct" or "scala media" and houses the sensitive organ of Corti, which detects pressure impulses caused by sound-induced vibrations of the eardrum and responds with electrical signals that are transmitted via the acoustic (vestibulocochlear) nerve to the brain.

Cross-sectional study: simplest variety of descriptive or observational epidemiological study that can be conducted on representative samples of a population. Basically it is a study that aims to describe the relationship between diseases (or other health-related states) and other factors of interest as they exist in a specified population at a particular time, without regard for what may have preceded or precipitated the health status found at the time of the study.

dB (Decibel): dimensionless unit expressing the relative loudness of sound on a logarithmic scale.

Diuretic: drug used to promote urine excretion.

Excitotoxicity: specific pathological process by which nerve cells can be injured. This phenomenon occurs when receptors are overactivated by excessive release of a neurotransmitter (chemical transferring signals between two nerve cells). In the specific case of glutamatergic excitotoxicity, the excess of the neurotransmitter glutamate induces a massive ion entry, which then is counterbalanced by an osmotic water inflow. This process leads to acute swellings, which may disconnect the junctions between adjacent nerve cells (synapses). The swellings can be reversible depending on the noise duration.

Hair cells (if not specified otherwise): sensory receptors of the auditory system in the ►organ of Corti of the inner ear. They are sandwiched between two membranes, the ►basilar membrane (bottom) and the ►reticular lamina (top). Auditory hair cells are characterised by a mechanosensitive hair bundle ("stereociliae") on their surface, which penetrates the ►reticular lamina. These stereociliae are bathed by endolymph, an extracellular fluid with a high potassium concentration. In the mammalian cochlea there are two anatomically and functionally distinct hair cell types: outer and inner hair cells. As opposed to inner hair cells (in humans, about 3,500 form a single row), the outer hair cells (approx. 20,000 are arranged in three rows) act as acoustic amplifiers by active vibrations of their cell bodies.

High-frequency audiometry (HFA): the technique of high-frequency audiometry (HFA) is nearly the same as for conventional ►audiometry but includes frequencies from 9,000 to 20,000 ►Hz.

Hz (Hertz): basic unit of frequency. 1 Hz is equal to one vibration per second. The healthy young human ear is capable of detecting sound waves with frequencies ranging from approximately 20 Hz to 20,000 Hz. The perception of the sound wave frequency is commonly known as the pitch of a sound. A high-pitch sensation is caused by a high-frequency sound wave, a low-pitch sensation by a low-frequency sound wave.

kHz (kilohertz): 1,000 ►Hz

Longitudinal study: an epidemiological longitudinal study investigates a group of people over a period of time. Most longitudinal studies examine associations between exposure to known or suspected causes of disease and subsequent morbidity or mortality. In the simplest design, a sample or cohort of subjects exposed to a risk factor is identified along with a sample of unexposed controls. The two groups are than followed up prospectively, and the incidence of disease in each is measured. By comparing the incidence rates, risks can be estimated.

Notch: permanent auditory threshold shift within a certain frequency range.

Organ of Corti: organ in the inner ear within the ►cochlea containing auditory sensory cells, or ►"hair cells" (see Figure 2)*:*

Otoacoustic emission (OAE): sound which is generated by the outer ►hair cells within the ►cochlea and which can be recorded by placing a microphone inside the outer ear. The response only emanates from the ►cochlea, but the outer and middle ear must be able to transmit the emitted sound back to the recording microphone. The objective and non-invasive otoacoustic emission test can be employed in humans and experimental animals, primarily to determine ►hair cell function.

Ototoxicity: chemical-induced reversible or irreversible effects that impair the senses of hearing or balance. These can be induced by disturbing the structures and/or the function of the inner ear (= auditory plus ►vestibular apparatus) and/or the connected neural pathways from the inner ear to (and including) the ►auditory cortex in the brain.

Presbycusis: constellation of age-related auditory deficits that include a bilateral loss of hearing sensitivity at high frequencies and a decreased ability to understand speech, particularly in the presence of background noise.

Pure tone audiometry (PTA): see ►audiometry

Reissner's membrane: membrane inside the ►cochlea of the inner ear (see Figure 2). Together with the basilar membrane it forms a compartment called "cochlear duct" or "scala media". This compartment is filled with a fluid ("endolymph") and contains the ►organ of Corti.

Reticular membrane: (reticular lamina): thin tissue sheet in the ►organ of Corti of the inner ear, through which the long protrusions (stereociliae) of the ►hair cells (see Figure 2) pass. Barrier for the specific extracellular endolymph fluid.

Retrocochlear impairment: anatomical impairment of the peripheral or central auditory nervous system behind the cochlea, namely the vestibulocochlear (acoustic) nerve and/or the ►auditory cortex in the brain).

Pure tone audiometry: measurement of an individual's hearing sensitivity for calibrated pure tones.

Sensorineural: relating to, or involving the sensory nerves, especially as they affect the hearing.

Spiral ganglion: agglomeration of nerve cells bodies in the ►cochlea constituting a switch point between the cochlear ►hair cells and the 8th cranial nerve (vestibulocochlear or acoustic nerve), which conducts the auditory stimuli to the brain.

Stria vascularis: specialised layer with numerous blood vessels on the outer wall of the cochlear duct, one of the three fluid-filled compartments of the ►cochlea (see Figure 2). The stria vascularis produces endolymph, a specific fluid for the cochlear duct.

Tinnitus: auditory symptom, which is characterised by sound perception ("ringing in the ear") in the absence of external sound stimulation. Noise exposure and ototoxic agents can cause tinnitus.

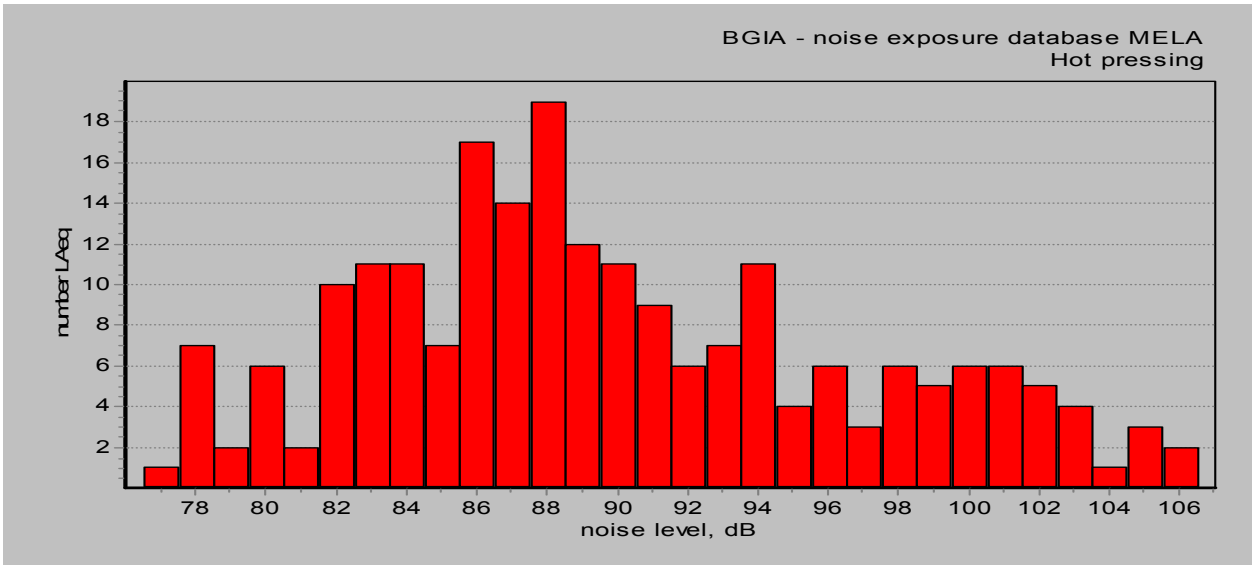
Vestibular apparatus: organ in the inner ear, adjacent to the ►cochlea. The vestibular apparatus collects signals which are decisive for the perception of balance, spatial orientation and movement. It consists of two parts: three semicircular canals, detecting angular and rotational acceleration, and the utricle and saccule, responsive to linear acceleration.

Vestibulo-cochlear apparatus: Hearing and equilibrium organ of the inner ear. It includes the ►cochlea and the ►vestibular apparatus.

10. Annex 1

Exposure to ototoxic substances and noise – selected according to working area: Hot pressing

Evaluations of the BGIA – MELA noise exposure database



Number of values: 214
Lowest value: 77.0 dB
Highest value: 105.7 dB

Arithmetic mean: 89.9 dB

Standard deviation: 6.9
Normal distribution: Yes

Evaluations of the BGIA – MEGA hazardous substances database

Period of time: 1990 – 2007

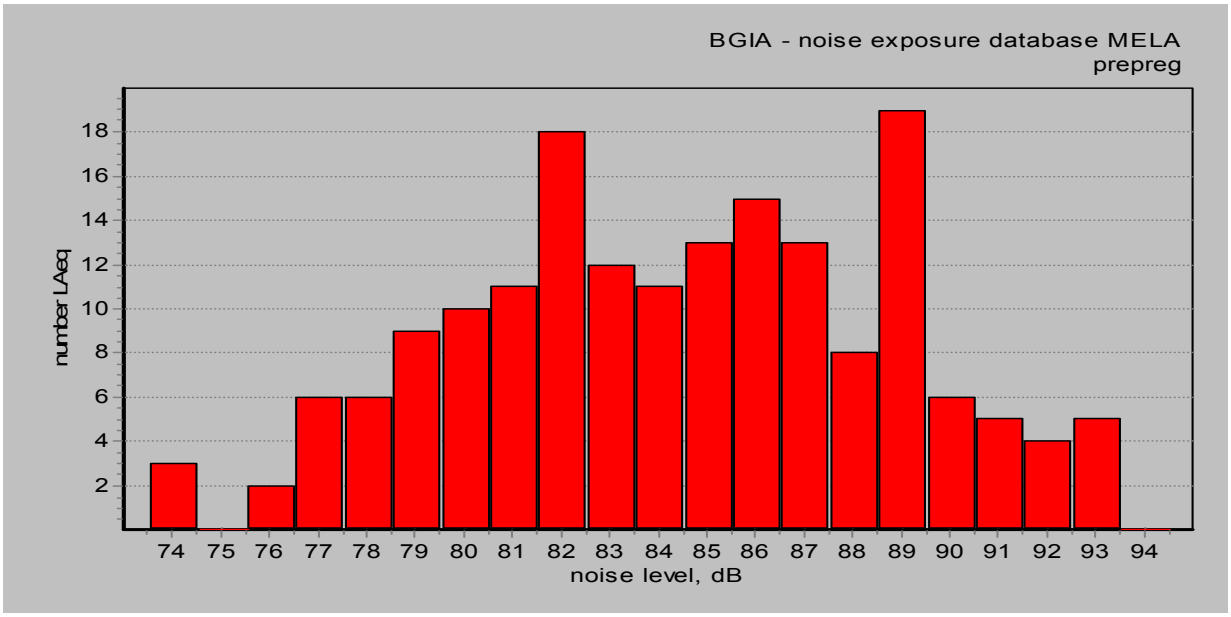
Exposure level per shift

Ototoxic substance OEL	Number of measured values	Number of companies	Below detection limit: Number %	Below limit value (OEL) %	Concentration (mg/m³)		
					50th percentile	90th percentile	95th percentile
Toluene 190 mg/m³	20	11	11 55	100	ADL	3.4	4.1
Xylene 440 mg/m³	13	8	7 53.8	100	ADL	2.92	30.21
Styrene 86 mg/m³	298	43	23 7.7	75.5	51	136.8	179
Ethylbenzene 440 mg/m³	4	3	1 25	100			

ADL: No percentile concentration is calculated because there are more values below the analytical detection limit (ADL) as represented by the percentage of this percentile OEL: Occupational Exposure Limit (Germany)

Exposure to ototoxic substances and noise – selected according to working area: Prepreg

Evaluations of the BGIA – MELA noise exposure database



Number of values: 176 Arithmetic mean: 84.4 dB Standard deviation: 4.4

Lowest value 74.0 dB Normal distribution: Yes

Highest value 93.5 dB

Evaluations of the BGIA – MEGA hazardous substances database

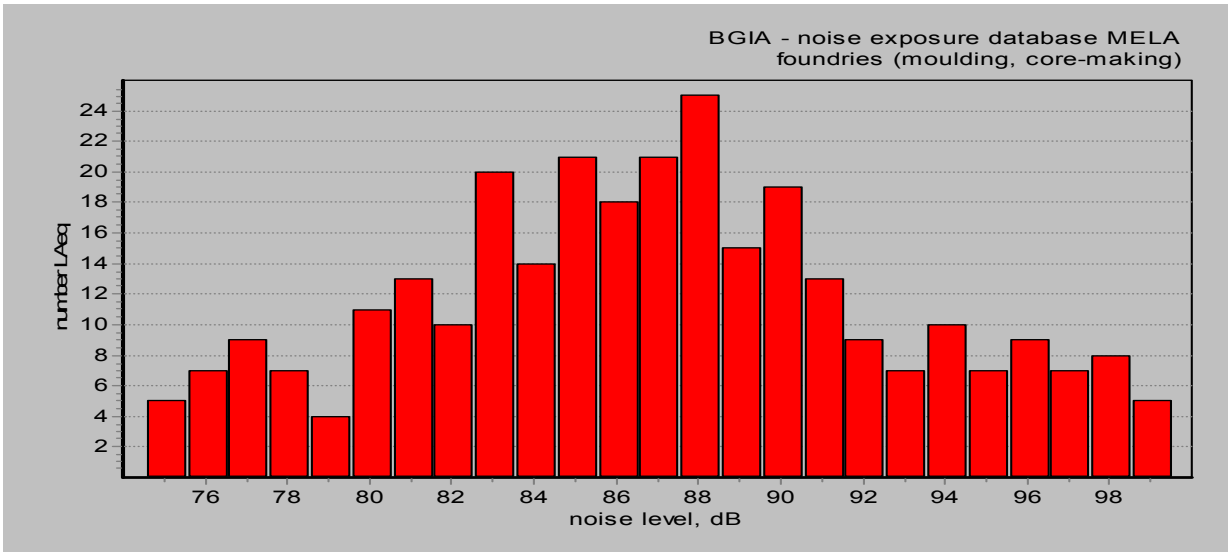
Period of time: 1990 – 2007 Exposure level per shift

Ototoxic substance OEL	Number of measured values	Number of companies	Below detection limit: Number %	Below limit value (OEL) %	Concentration (mg/m³)		
					50th percentile	90th percentile	95th percentile
Toluene 190 mg/m³	23	10	15 65.2	100	ADL	64.9	114.35
Xylene 440 mg/m³	15	8	13 86.7	100	ADL	0.55	1.137
Styrene 86 mg/m³	219	41	0	53.4	79.5	207.3	245.15

ADL: No percentile concentration is calculated because there are more values below the analytical detection limit (ADL) as represented by the percentage of this percentile OEL: Occupational Exposure Limit (Germany)

Exposure to ototoxic substances and noise – selected according to working area: moulding and core-making in foundries

Evaluations of the BGIA – MELA noise exposure database



Number of values: 294 Arithmetic mean: 86.9 dB Standard deviation: 5.8
Lowest value: 75.0 dB : Normal distribution: Yes
Highest value: 99.0 dB

Evaluations of the BGIA – MEGA hazardous substances database

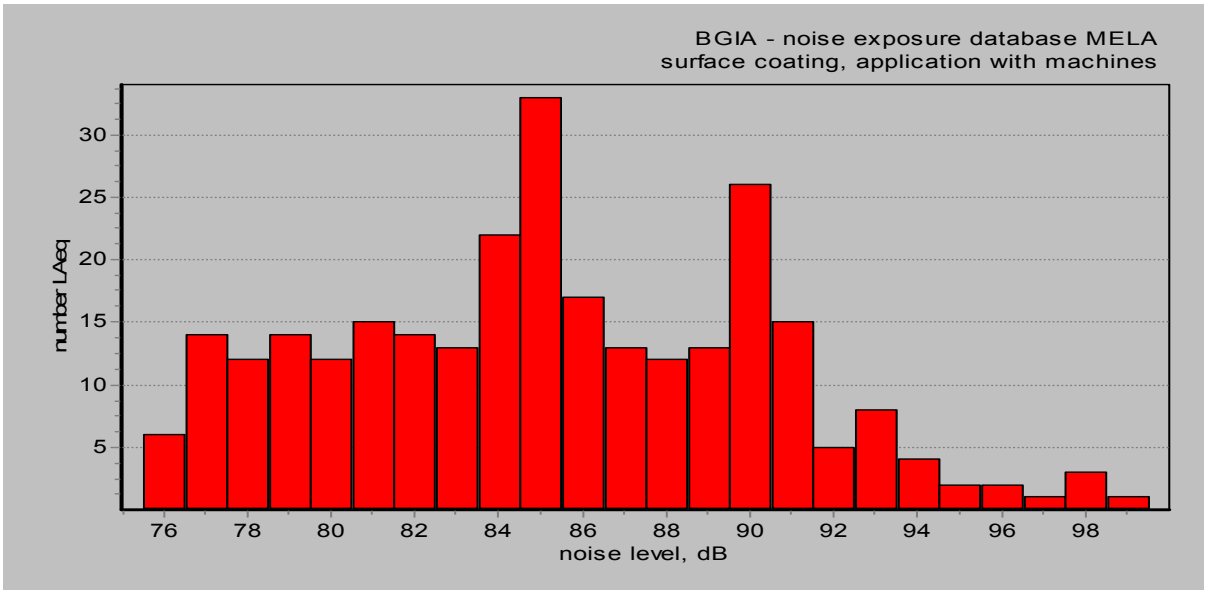
Period of time: 1990 – 2007 Exposure level per shift

Ototoxic substance OEL	Number of measured values	Number of companies	Below detection limit: Number %	Below limit value (OEL) %	Concentration (mg/m³)		
					50th percen-tile	90th percen-tile	95th percen-tile
Toluene 190 mg/m³	50	33	15 30	100	2.2	8.1	11
Carbon monoxide 35 mg/m³	14	11	1 7.1	71.4	6.44	63.24	67.044

ADL: No percentile concentration is calculated because there are more values below the analytical detection limit (ADL) as represented by the percentage of this percentile OEL: Occupational Exposure Limit (Germany)

Exposure to ototoxic substances and noise – selected according to working area: Surface coating, application with machines

Evaluations of the BGIA – MELA noise exposure database



Number of values: 277 Arithmetic mean: 85.2 dB Standard deviation: 5.1
Lowest value: 76.0 dB Normal distribution: Yes
Highest value: 99.0 dB

Evaluations of the BGIA – MEGA hazardous substances database

Period of time: 1990 – 2007 Exposure level per shift

Ototoxic substance OEL	Number of measured values	Number of companies	Below detection limit: Number %	Below limit value (OEL) %	Concentration (mg/m³)		
					50th percentile	90th percentile	95th percentile
Ethylbenzene 440 mg/m³	850	353	365 42.9	99.9	1.2	11	18.5
Toluene 190 mg/m³	1099	366	310 28.2	96.4	5	71.1	138.1
Xylene 440 mg/m³	1435	544	580 40.4	99.7	1.9	25	48.05
Styrene 86 mg/m³	129	40	22 17.1	77.5	19	155.2	180.95

ADL: No percentile concentration is calculated because there are more values below the analytical detection limit (ADL) as represented by the percentage of this percentile OEL: Occupational Exposure Limit (Germany)