1. Introduction

Exposure to chemicals in the workplace can lead to occupational chemical-induced hearing loss, as many chemicals have been internationally recognised as hazardous to hearing. A number of studies have demonstrated that, similar to noise, some chemicals not only affect the sensory organ of the auditory system (the cochlea) but also lead to adverse effects in central auditory structures. Morata and Lemasters (1995) suggested that the adverse auditory effects of chemicals such as solvents are due to a combination of oto-and neuro-toxicity. Oto-toxicity induces outer hair cell (OHC) dysfunction in the cochlea (similar to the effects of noise), whereas neuro-toxicity induces central auditory dysfunction. The main audiological sign of oto-toxicity is poorer hearing thresholds than expected relative to age. Audiological signs of neuro-toxicity may or may not include poorer hearing thresholds, in addition to difficulties discriminating sounds, such as speech, particularly in adverse listening conditions.

The aim of this review is to provide an in-depth discussion of occupational chemical-induced hearing loss, taking into consideration ototoxic agents such as solvents, pesticides and metals, and their interaction with noise. Contemporary findings from research conducted in animals and humans are included here. Also, research findings from the authors with regard to the effect of exposure to mixtures of solvents on the peripheral and central auditory system will be addressed. Finally, in the section on international legislation of occupational chemical-induced hearing loss, a review of current legislation in a number of countries is presented.

2. Solvent-induced hearing loss

2.1 Overview of solvents

A solvent is a liquid used to dissolve other substances. Most solvents are colourless liquids at room temperature that volatise easily and have strong odours. Solvents are most commonly inhaled in their volatised form and absorbed through the respiratory tract. Organic solvents are widely used around the world and many different industrial processes require their use. Table 1 summarises the main organic solvents and their common industrial uses.
### Table 1. Main industrial uses of some selected organic solvents.

<table>
<thead>
<tr>
<th>Organic solvent</th>
<th>Industrial uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>Electroplating, adhesive manufacture, laboratory chemicals, metal degreasing, paint manufacture, paint stripping, paper coating, pharmaceuticals manufacture, printing, rubber manufacture, wood stains and varnishes, and footwear manufacture.</td>
</tr>
<tr>
<td>Styrene</td>
<td>Fabrication of fibreglass boats, pulp and paper manufacture and in plastics, resins, coatings, and paint manufacture.</td>
</tr>
<tr>
<td>Xylene</td>
<td>Laboratory chemicals, machinery manufacture and repair, paint manufacture, paint stripping, paper coating, pesticide manufacture, pharmaceuticals manufacture, printing, rubber manufacture, and in wood stains and varnishes.</td>
</tr>
<tr>
<td>Ethyl benzene</td>
<td>Machinery manufacture and repair, paint manufacture, paper coating, rubber manufacture, wood stains and varnishes.</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>Electroplating, integrated iron and steel manufacture, machinery manufacture and repair, metal degreasing, pulp and paper manufacture.</td>
</tr>
</tbody>
</table>

#### 2.2 Evidence of the adverse auditory effects of solvents from animal studies

Organic solvents such as toluene, styrene, xylene, and ethyl benzene have been identified as inducing damage to the outer hair cells (OHCs) in the cochlea of experimental animals (Campo et al., 1997; Cappaert et al., 1999; Cappaert et al., 2000; Crofton et al., 1994; Johnson & Canlon, 1994; Loquet et al., 1999; McWilliams et al., 2000; Pryor et al., 1987; Sullivan et al., 1988; Yano et al., 1992). The damage caused by these solvents in its early stages occurs in the third row of external OHCs and it then progresses toward the second and first rows. The mid-range of audible frequencies for the rat is affected first and according to some authors the damage continues toward the apical zone of the cochlea (Campo et al., 1997; Johnson & Canlon, 1994). The damage impacts mainly at the mid-frequency region of experimental animal cochleae, and this distinguishes the auditory effects induced by solvents such as toluene from those observed with ototoxic drugs such as aminoglycoside antibiotics and cisplatin (Liu et al., 1997) which mainly affect the apical region of the cochlea.

In the case of trichloroethylene, cochlear histopathology has revealed loss of spiral ganglion cells, mainly in the middle turn, and also an inconsistent loss of hair cells (Fechter et al., 1998).

Rebert et al. (1995) observed an increase in auditory brainstem response (ABR) latencies in rats after exposure by inhalation to pairs of solvents (trichloroethylene and toluene; xylene and trichloroethylene; xylene and chlorobenzene; chlorobenzene and toluene). Results of this study indicated an additive rather than a synergistic or antagonistic interaction. Other studies have also demonstrated additive ototoxic effects for styrene and trichloroethanol (Rebert et al., 1993), and styrene and ethanol (Loquet et al., 2000). This additive effect, as
opposed to the synergistic effect found with combinations of solvents, implies that the mechanism of ototoxicity for these solvents may be similar.

Research has also demonstrated that rats simultaneously exposed to both toluene and noise suffer a more severe hearing loss than the summated hearing loss obtained from an equivalent exposure level to each agent alone (Brandt-Lassen et al., 2000; Lataye & Campo, 1997). The synergistic interaction between noise and toluene occurs when both agents are presented simultaneously, or when toluene is immediately followed by noise. Lataye & Campo (1997) claimed that even if the coexistence of both mechanisms (the ototoxicity induced by toluene and that induced by noise) potentiates cochlear effects, it seems nevertheless that there are no other mechanisms induced by a simultaneous exposure to noise and toluene. Combined exposure to noise and styrene in rats has also shown the existence of synergism between these two agents (Lataye et al., 2000; Makitie et al., 2003).

Evidence from Lataye et al. (2005) suggests that conditions such as level of activity of the rats may be an important factor in the mechanism of styrene-induced hearing loss. The researchers found that the same degree of styrene-induced hearing loss can be obtained by using concentrations approximately 200 ppm lower in active rats than in sedentary rats. This may explain why the studies conducted in experimental animals require higher solvent concentrations to induce hearing loss than in humans. Workers are not sedentary in the workplace. They usually are moving from one place to another, or manipulating machinery. Increased activity implies greater consumption of oxygen compared to sedentary conditions. The study of Lataye et al. (2005) has provided some explanation for the variations in concentrations that are needed to induce auditory dysfunction in experimental animals and humans. In animal models it is possible to control most of the variables; however, in humans many factors such as physical activity cannot be controlled experimentally.

Lataye et al. (2007) found a striking increase (4.2 dB) in the cochlear microphonic potential amplitude which was followed after left-carotid administration of toluene in experimental animals. An increase in the cochlear microphonic potential relates to the inhibition of the efferent control of the OHCs, and thus a lack of inhibition in the mechanical response of the OHCs to electrical signals. Lataye et al. (2007) suggested that toluene inhibits the acetylcholine (Ach) receptors located in the efferent auditory system (medial olivocochlear bundle) that mediates the contraction of the OHCs in the cochlea. Similarly, Campo et al. (2007) found that toluene may inhibit the Ach receptors of the efferent motor neurons located near the facial nerve nuclei that mediate the middle ear muscle systems. These two studies represent the first evidence from animal models that solvents may induce central auditory dysfunction at the level of the efferent auditory system.

In summary animal data demonstrates that solvents in isolation can induce OHC loss, and in the case of trichloroethylene, spiral ganglion cell loss—mainly in the middle turn of the cochlea—is observed. Also, it has been observed that solvents such as toluene adversely affect the efferent auditory system associated with the control of the contraction of the OHCs as well as with the mediation of the middle ear acoustic reflex. Synergism between solvents and noise has been observed in rats.
2.3 Evidence of the adverse effects of solvents on pure-tone thresholds: Studies on humans

Exposure to a mixture of solvents may induce hearing loss in humans (Morata, Engel et al., 1997) and, at some frequencies, solvents may damage the inner ear to a much greater extent than noise exposure (Sliwinska-Kowalska et al., 2000). Hearing loss induced by solvents has been found in workers exposed to a mixture of toluene, ethyl acetate and ethanol (Morata, Engel et al., 1997), and xylene and ethyl acetate (Sliwinska-Kowalska et al., 2000). Sliwinska-Kowalska et al. (2000) found hearing loss in 30% of workers exposed to organic solvents, in 20% of noise-exposed subjects, and in only 6% of non-exposed subjects. The relative risk value for hearing loss in workers exposed to solvents was greater (RR=9.6) in comparison to workers exposed only to noise (RR=4.2). Sulkowski et al. (2002) found high frequency sensorineural hearing loss in 42% of workers exposed to a mixture of solvents (not specified by the authors). In contrast, only 5% of the subjects in the control group (age-matched non-exposed subjects) showed hearing loss. Studies in populations of workers mainly exposed to one type of solvent have been also conducted. High frequency (8-16 kHz) hearing loss has been suggested to be associated with styrene dose exposure in humans. In the study of Muijser et al. (1988), high frequency hearing thresholds were significantly increased in those workers with the greatest exposure to styrene. Also, Morata et al. (2002) found an additive damage effect of styrene for pure-tone thresholds at 2, 3, 4 and 6 kHz. The odds ratio for hearing loss estimated by Morata et al. (2002) was 2.44 times greater for each increment of 1 mmol of mandelic acid (a biologic marker of styrene exposure) per gram of creatinine in urine. Morata et al. (2002) suggested that styrene can affect the mid-audiometric frequency of 2 kHz, which is in agreement to the findings of Sliwinska-Kowalska et al. (2001). Morata et al. (2002) also stated that styrene even below recommended values had a toxic effect on the auditory system.

Sliwinska-Kowalska et al. (2003) found a 4-fold increase in the odds of developing hearing loss in subjects exposed to styrene. In this study the mean hearing thresholds (adjusted for age, gender, and exposure to noise) were significantly higher in a solvent-exposed group than in an unexposed reference group at all frequencies tested. A positive linear relationship was observed between average working life exposure to styrene concentrations and hearing thresholds at 6 and 8 kHz. Also, the effects of carbon disulphide on hearing have been explored (Morata, 1989). Results of pure-tone audiometry indicated a 66.7% prevalence of hearing loss among exposed workers and only 6.6% of this was attributed to non-occupational causes (Morata, 1989).

The possible synergism of combined exposure to solvents and noise on hearing has not been consistently identified in human studies. Some researchers have failed to find a synergistic effect between these agents on hearing. Jacobsen et al. (1993) in a cohort study showed a dominant effect of noise and no additional hearing risk as a result of solvent exposure. However, workers exposed only to solvents had a significantly increased risk ratio for hearing loss. Sliwinska-Kowalska et al. (2001), in a study conducted involving paint and lacquer factory workers, were not able to show any additional risk of hearing loss with a combined exposure to noise and a mixture of organic solvents, when compared with isolated exposure to solvents only. However, Polizzi et al. (2003) reported a case of a painter exposed to noise and a mixture of organic solvents. The authors described an unusual
pattern of hearing loss, which was characterised by a maximum loss in the low and mid-frequencies. The researchers suggested that this pattern may be induced by a possible synergistic effect of noise exposure combined with solvents. However, this finding may have limited application as the data was collected from a single subject. Other evidence supporting the claim that solvents in combination with noise may have a synergistic effect on the auditory system in humans was reported by Sliwinska-Kowalska et al. (2003). They found an increase in the odds ratio for hearing loss of 21.5 in workers exposed to styrene, toluene, and noise. These authors suggested that a synergistic action of multiple ototoxic agents with noise was evident.

A recent multicentre, cross-sectional study (Morata et al. 2011) of workers from Sweden, Finland, and Poland found an association between styrene exposure and poorer hearing thresholds than predicted by individuals’ age (when compared with ANSI S3.44 annexes A and B). The effect of noise exposure, with a mean which varied across centres between 80 and 84 dBA, did not have a significant effect on hearing, except when in combination with styrene.

Hearing loss induced by simultaneous exposure to noise and mixed solvents in the aviation industry was studied by Kim et al. (2005). This study found a prevalence of hearing loss of 54.9% among workers exposed to both agents simultaneously; 17.1% among workers exposed only to noise; 27.8% among workers only exposed to a solvent mixture; and 6% among non-exposed workers. Relative risks adjusted for age were estimated to be 4.3 for the noise-only group, 8.1 for the noise and solvents group, and 2.6 for the solvents-mixture group. Also, Kaufman et al. (2005) found that subjects exposed to noise and jet fuel for three years had an increase in adjusted odds for hearing loss (RR=1.7), and in those with a history of 12 years exposed to both agents the odds for hearing loss increased to 2.41. This study found that the effects of jet fuel exposure on hearing were statistically non-significant for more than 12 years of combined noise and jet fuel exposure. The authors suggested a plateau effect for jet fuel exposure and/or that the noise-induced hearing loss may become more important for those continuing to have exposure to both agents.

All these studies provide evidence that solvents may induce peripheral hearing loss in human subjects. However, none of the previously mentioned studies provides evidence of central auditory dysfunction induced by solvent exposure or of the precise cochlear origin of such hearing losses. They only suggest poorer hearing thresholds among solvent-exposed subjects in comparison to non-exposed subjects. Next we discuss the scientific evidence for central auditory dysfunction associated with solvent exposure.

2.4 Evidence of the adverse effects of solvents on the central auditory system: Studies on humans

Many studies have found dysfunction of the central auditory nervous system (CANS) in workers exposed to a mixture of solvents (Fuente et al., 2006; Fuente & McPherson, 2007; Laukli and Hansen, 1995; Moen et al., 1999; Niklasson et al., 1998; Ödkvist et al., 1987; Ödkvist et al., 1992; Pollastrini et al., 1994; Varney et al., 1998). Fuente et al. (2006), Fuente & McPherson (2007), and Fuente (2008) have shown that workers exposed to a mixture of solvents (toluene, xylene and methyl ethyl ketone) may acquire central auditory dysfunction
as evidenced by abnormal results for a set of behavioural central auditory processing tests. Varney, Kubu et al. (1998) found abnormal results for a dichotic listening test among solvent exposed subjects in comparison to previously reported norms and to a control group of subjects. The authors claimed that dichotic listening appeared to be a useful tool in the assessment of solvent-exposed workers, particularly in those who have had intermediate levels of exposure and who do not show mental status deficits of disabling severity.

Also, different studies have been conducted in workers exposed to solvents utilising electrophysiological techniques. Workers exposed to toluene obtained statistically significant higher absolute latencies and inter-peak latencies (IPL) between waves of the ABR (I-III IPL; I-V IPL; III-V IPL) than a non-exposed group of workers matched for gender and age (Abbate et al., 1993). Additional evidence of toluene-induced central auditory dysfunction in humans using ABR was shown by Vrca et al. (1996). Workers exposed to low concentrations of toluene obtained a significant decrease in all wave amplitudes of auditory evoked potentials. However, a study carried out by Schäper et al. (2003) did not find a toluene effect on ABR results in a group of workers exposed to toluene up to 50 parts per million (ppm). The authors suggested that toluene may induce central auditory dysfunction at levels above 50 ppm.

ABR abnormalities due to carbon disulphide exposure have also been studied (Hirata et al., 1992). A high percentage of workers exposed to carbon disulphide for more than 240 months obtained prolonged IPL for the ABR components III-V (Hirata et al., 1992). Other electrophysiological measures such as P300 (a long latency auditory evoked potential) have also been utilised in solvent-exposed subjects. Vrca et al. (1997) found, in a group of workers exposed to low concentrations of toluene, prolonged latencies and lower amplitudes in the P300 response in comparison to a control group. Also, Moen et al. (1999) examined the P300 component in a group of workers exposed to low levels of organic solvents in a paint factory and in a control group of non-exposed workers. The results indicated that the P300 latency was prolonged among the exposed workers compared to the control group before the summer vacation, and also, in the exposed group the P300 latency was significantly longer before the summer vacation than after. Similar results were found by Steinhauer et al. (1997).

More recently, Draper and Bamiou (2008) presented a case study of a person exposed to xylene who presented with auditory neuropathy as evidenced by abnormal ABR results and presence of otoacoustic emissions (OAEs). The patient presented with a gradual deterioration in his ability to hear in difficult acoustic environments and also to hear complex sounds such as music, over a 40-year period. His symptoms began after exposure to xylene, and in the absence of any other risk factor.

Fuente et al. (2011) conducted an investigation of central auditory functioning in normal-hearing, solvent-exposed subjects compared to normal-hearing, non-exposed subjects with a comprehensive battery of behavioural central auditory function assessment procedures. Forty-six normal-hearing, solvent-exposed subjects and 46 normal-hearing, non-exposed subjects were investigated. The test battery comprised of pure-tone audiometry (PTA), Dichotic Digits (DD), Pitch Pattern Sequence (PPS), Filtered Speech (FS), Random Gap Detection (RGD), Masking Level Difference (MLD), and Hearing-in-Noise (HINT) tests. Analyses of covariance were performed to compare the mean values of the dependent variables (results for DD, PPS, FS, RGD, MLD, and HINT) between solvent-exposed and
non-exposed subjects. Age and average hearing thresholds (500-8000 Hz) were included in the analyses as covariates. Although all subjects had normal-hearing thresholds, significant differences for DD, PPS, FS, and RGD results were found between groups. Solvent-exposed participants presented with poorer results adjusted for age and hearing thresholds in comparison to non-exposed subjects.

These results are in agreement with our previous studies in which significant differences between solvent-exposed and non-exposed subjects arose for the DD, RGD, HINT, PPS, and FS tests. Fuente et al. (2008) also showed that in a group of 100 workers exposed to a mixture of solvents and 100 non-exposed workers, solvents were significantly associated with poorer pure-tone thresholds, lower amplitudes of transient evoked otoacoustic emissions (TEOAEs), and poorer results for central auditory functioning tests. Recently, in a study investigating a group of 30 medical laboratory workers exposed to xylene and a control group of non-exposed workers, Fuente (2010) found significant differences between groups for ABR results. Xylene-exposed workers presented with longer ABR latencies than non-exposed workers. Figure 1 summarises the results of our studies in different populations of workers exposed to solvents.

From Figure 1, it is possible to observe that different procedures can be utilised to evaluate possible adverse auditory effects of solvents on the auditory system. Taking into consideration that solvents may affect a wide range of aspects of audition, an approach using a comprehensive battery of tests is required to monitor hearing in solvent-exposed individuals. Table 2 summarises the audiological procedures that can be incorporated in the test battery to evaluate solvent-induced auditory dysfunction. The tests that have been included in Table 2 are those who have been shown to be sensitive to detect differences between solvent exposed and non-exposed subjects, based on our previous studies and on the evidence provided by multiple studies, as discussed above.
### Table 2. Recommended audiological tests for the evaluation of hearing in solvent-exposed subjects.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Auditory-related aspects</th>
<th>Procedure references</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABR</td>
<td>Status of the brainstem auditory pathways.</td>
<td>Arnold, 2000</td>
</tr>
<tr>
<td>Filtered speech</td>
<td>Low redundancy monaural speech discrimination.</td>
<td>Bellis, 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wilson &amp; Mueller, 1984</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keith, 2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keith, 2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Musiek, 1994</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Musiek, 1983</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a,b</td>
</tr>
<tr>
<td>Hearing-in-noise test (HINT)</td>
<td>Speech discrimination in the presence of background noise.</td>
<td>Nilsson et al.,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1994</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laroche et al.,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2003</td>
</tr>
</tbody>
</table>

### 3. Hearing loss associated with occupational exposure to pesticides

#### 3.1 Overview of pesticides

The Food and Agriculture Organization (FAO, 2003, Page 6) has defined pesticides as “any substance or mixture of substances intended for preventing, destroying or controlling any pest, including vectors of human or animal disease, unwanted species of plants or animals causing harm during or otherwise interfering with the production, processing, storage, transport or marketing of food, agricultural commodities, wood and wood products or animal feedstuffs, or substances which may be administered to animals for the control of insects, arachnids or other pests in or on their bodies. The term includes substances intended for use as a plant growth regulator, defoliant, desiccant or agent for thinning fruit or preventing the premature fall of fruit, and substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport”.

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Most pesticides can be classified into chemical families. Table 3 summarises the four main chemical categories of pesticides according to the US Environmental Protection Agency. Pesticides are also often referred to according to the type of pest they control (e.g. fungicides, herbicides, insecticides, rodenticides).

<table>
<thead>
<tr>
<th>Pesticide</th>
<th>Main characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organophosphates</td>
<td>Developed in the 19th century and extensively used in World War II as nerve agents.</td>
</tr>
<tr>
<td></td>
<td>Most commonly used pesticides today and mainly insecticides.</td>
</tr>
<tr>
<td></td>
<td>Affect the nervous system of the target agent.</td>
</tr>
<tr>
<td>Carbamates</td>
<td>First introduced in the 1950s.</td>
</tr>
<tr>
<td></td>
<td>Affect the nervous system of the target agent.</td>
</tr>
<tr>
<td>Organochlorides</td>
<td>Extensively used in the past 60 years.</td>
</tr>
<tr>
<td></td>
<td>Organochloride pesticides such as dichloro-diphenyl-trichloroethane (DDT) have been widely banned as they represent serious environmental and human health risks.</td>
</tr>
<tr>
<td>Pyrethroids</td>
<td>Developed for wide commercial use in the 1970s.</td>
</tr>
<tr>
<td></td>
<td>They are used as insecticides in gardens, and with pets and livestock.</td>
</tr>
</tbody>
</table>

Table 3. Main chemical families of pesticides and their characteristics.

3.2 Scientific evidence of pesticide-induced auditory dysfunction

Studies on the auditory effects of exposure to pesticides are rare. Harell et al. (1978) were one of the first research groups to describe pesticide-induced hearing loss. The authors reported a case of a 27-year-old male who was referred for a re-evaluation of his bilateral hearing loss. The onset of his hearing loss was more than six years before the follow-up hearing assessment, and it developed after he sprayed several fruit trees for 15-20 minutes using a preparation containing 7.5% malathion and 15% methoxychlor. After intoxication with low levels of insecticides, the patient developed a permanent bilateral profound hearing loss with the presence of tinnitus, and also peripheral neuropathies in the extremities. Other initial signs such as renal failure and hepatic dysfunction gradually improved.

A number of cross-sectional human studies have found hearing loss associated with the use of insecticides. A study comparing two groups of individuals exposed to organophosphates with different levels of pseudocholinesterase activity reported peripheral neuropathies in the group with low values of pseudocholinesterase. Pseudocholinesterase is an enzyme involved in the breakdown of acetylcholine and it is mainly found in the plasma and liver. Reduced plasma levels of pseudocholinesterase are an indicator of excessive organophosphate absorption. Both groups of individuals with low and high levels of pseudocholinesterase had sensorineural hearing loss, ranging in severity from low to moderate (Ernest et al., 1995).
Mac Crawford et al. (2008) investigated self-reported hearing loss in licensed private pesticide applicators enrolled in the Agricultural Health Study in 1993-1997 in Iowa and North Carolina, USA. Results showed that exposure to herbicides, fungicides, or fumigants was not associated with hearing loss. However, organophosphates were associated with hearing loss, with a 17% increase in odds in the highest quartile of exposure. Carbamates, organochlorines and pyrethroids were not associated with hearing loss. The authors also found a positive association between self-reported hearing loss and several general measures of pesticide exposure such as high pesticide exposure events, pesticide poisoning and medical treatment for pesticide exposure. Additionally, the association of pesticide exposure with hearing loss was not modified or confounded by age. The authors concluded that the results of their study suggest that exposure to insecticides and, in particular, organophosphates, may contribute to hearing loss.

Guida et al. (2010) studied 40 male individuals exposed to malathion and noise and 40 individuals exposed only to noise. Individuals exposed to malathion and noise presented with significantly worse hearing thresholds for 4 kHz (both ears) and 3 kHz (left ear) than individuals exposed only to noise. Also, more than 60% of individuals exposed to malathion and noise had hearing loss in comparison to 42% of individuals exposed only to noise.

Adverse central auditory effects associated with insecticide exposure have also been found. Teixeira et al. (2002) studied a group of 98 male workers with a minimum of 3 years insecticide exposure who used organophosphate and pyrethroid compounds, and a control non-exposed group of 54 administrative workers. The insecticide-exposed workers were divided into two subgroups, insecticide-exposed only, and insecticide-and-noise-exposed (with noise levels above 90 dBA). Two procedures to evaluate central auditory function were utilised, the pitch pattern sequence (PPS) and duration pattern sequence (DPS) tests. Results showed that 56% of insecticide-exposed workers had findings for PPS and/or DPS below normal ranges, and only 7% of the control non-exposed workers had results below normal ranges, for the DPS test only. Statistically significant differences for PPS and DPS test results between insecticide only exposed workers and control non-exposed workers, and also between insecticide-and noise-exposed workers and control non-exposed workers were found. Insecticide-exposed workers performed significantly worse than non-exposed control workers in both PPS and DPS tests. Teixeira et al. (2002) concluded that chronic exposure to pyrethroid and organophosphate insecticides seems to affect central auditory function. They also suggested that central auditory functioning tests should be incorporated in the audiological evaluation of persons exposed to known neurotoxic substances.

4. Hearing loss associated with occupational exposure to metals

4.1 Overview of metals

Currently there are 86 known metals. Before the 19th century only 24 of these metals had been discovered. Metals are used in their pure forms, in the form of compounds of two or more metals (alloys), and in the form of metal salts. Table 4 summarises the industrial uses of some common selected metals.
### Metal Industrial uses

<table>
<thead>
<tr>
<th>Metal</th>
<th>Industrial uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper</td>
<td>Power generation and transmission of electricity, electrical wires, roofing and plumbing, and industrial machinery.</td>
</tr>
<tr>
<td>Lead</td>
<td>Car batteries, ballast keel of sailboats and scuba diving weight belts, soldering and as electrodes in the process of electrolysis, polyvinyl chloride (PVC) plastic that covers electrical cords, glazing bars for stained glass or other multi-lit windows.</td>
</tr>
<tr>
<td>Mercury</td>
<td>Manufacture of industrial chemicals, electronic applications, cosmetics, manufacturing of thermometers and fluorescent lamps, medical applications such as dental amalgams, as part of preservatives in vaccines, and topical antiseptics.</td>
</tr>
<tr>
<td>Zinc</td>
<td>Galvanization, manufacturing of batteries, in copper-base alloys. Manufacture of zinc sheets to be used for sheathing or roofing.</td>
</tr>
<tr>
<td>Lithium</td>
<td>Manufacture of batteries, ceramics, glass and pharmaceuticals. In rubber and thermoplastics industries, air treatment and in primary aluminium production.</td>
</tr>
</tbody>
</table>

Table 4. Main industrial uses of some selected metals.

### 4.2 Scientific evidence of metal-induced auditory dysfunction

Evidence from animal studies suggests ototoxic effects may be induced by lead. Lasky et al. (1995) in a study conducted in monkeys found abnormal distortion product otoacoustic emissions and lower than normal ABR amplitudes in monkeys with the highest blood concentrations of lead.

Hirata and Kosaka (1993) studied a group of lead exposed human subjects and a control non-exposed group through ABR, among other tests. Results showed that the mean IPL between components III and V of the ABR of lead-exposed workers was significantly prolonged compared with that of the control group.

Counter and Buchanan (2002) studied ABR and pure-tone thresholds as biomarkers for neuro-ototoxicity in adult workers with chronic lead intoxication from long-term exposure in ceramic-glazing work. Blood samples collected from 30 subjects showed higher biological concentrations than the limits established by the World Health Organization (WHO). Sensorineural hearing loss for the frequencies 2, 3, 4, 6, and 8 kHz was found among lead-exposed workers. ABR results showed delayed absolute latencies consistent with sensorineural hearing loss among individuals with elevated blood lead. Counter and Buchanan (2002) concluded that noise and lead intoxication were the cause of the hearing loss observed in the sample of subjects studied.

Buchanan et al. (1999) investigated pure-tone thresholds and distortion product otoacoustic emissions (DPOAEs) in 14 children (28 ears) and 5 adults (10 ears) living in a highly lead-contaminated environment in remote villages in the Andes Mountains of Ecuador. Blood lead levels for the children were higher than the U.S. Centers for Disease Control and Prevention's toxic level. Results showed normal hearing thresholds and presence of
DPOAEs. No correlation of DPOAEs with blood lead level was found among the children. The group of adults had diminished DPOAEs which were consistent with noise-related hearing loss.

Murata et al. (1993) examined ABR and event-related potential (P300) recordings, along with non-audiological assessments in lead workers. The sample consisted of 22 gun metal foundry workers occupationally exposed to lead, zinc, and copper. Among the workers with higher blood lead concentrations, the latencies of P300 were significantly prolonged when compared with a gender- and age-matched control group. Both ABR and P300 latencies were significantly correlated with the indicators of lead absorption among these workers.

Discalzi et al. (1992) investigated the effects of industrial exposures to lead and mercury on the brainstem auditory pathway through ABR. The study included 22 workers exposed to lead, 8 workers exposed to mercury and 2 control groups of age- and gender-matched subjects never exposed to neurotoxic substances. The I-V IPL was examined. Results showed that both mercury and lead exposed workers had a significant delay for the I-V IPL. The researchers also found that those subjects with the highest level of lead in blood had a longer I-V IPL compared to workers with lower levels of lead in blood.

5. International legislation

It is well documented that workplace noise exposure is a significant health hazard that leads to permanent, occupational noise-induced hearing loss. For this reason, many countries have developed national exposure standards for occupational noise, based on levels of exposure which are considered safe for human hearing. Likewise, exposure to chemicals in the workplace can lead to occupational chemical-induced hearing loss, as many of these chemicals have been internationally recognised as being hazardous to hearing. However, unlike noise exposure, standards for permissible levels of exposure to chemicals such as solvents in the US and other countries do not consider the adverse effects of chemicals on human hearing. This is because human exposure-response relationships remain unclear and thus chemical exposure standards have not been modified to reduce the risk of hearing impairment. Currently, recommended or mandatory workplace exposure limits (OELs) have been developed in many countries for airborne exposure to gases, vapours and particulates. The most widely used limits, threshold limit values (TLVs), are those issued in the USA by the American Conference of Governmental Industrial Hygienists (ACGIH). Table 5 shows the current US permissible exposure limits for some organic solvents according to different US organisations.

Taking into consideration the ototoxicity of many chemicals, some international bodies and governments have issued guidelines or recommendations regarding the ototoxicity of chemicals alone or when combined with noise. In the WHO 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 and metal dust is noted and it is suggested that more stringent criteria than those specified as being standard in the document should be applied. Ototoxic properties are acknowledged on the International Chemical Safety Cards (a joint programme of the International Labour Organization, WHO, and United Nations; Obadia, 2003) only for toluene, xylene and potassium bromate.
Table 5. Permissible exposure limits (PEL) to selected organic solvents according to different organisations in the U.S. PPM: parts per million; OSHA: Occupational Safety and Health Administration; NIOSH: National Institute for Occupational Safety and Health; ACGIH: American Conference of Industrial Hygienists.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>OSHA</th>
<th>NIOSH</th>
<th>ACGIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>200 ppm</td>
<td>100 ppm</td>
<td>50 ppm</td>
</tr>
<tr>
<td>Styrene</td>
<td>100 ppm</td>
<td>50 ppm</td>
<td>20 ppm</td>
</tr>
<tr>
<td>Xylene</td>
<td>100 ppm</td>
<td>100 ppm</td>
<td>100 ppm</td>
</tr>
<tr>
<td>Ethyl benzene</td>
<td>100 ppm</td>
<td>100 ppm</td>
<td>100 ppm</td>
</tr>
<tr>
<td>Carbon disulfide</td>
<td>20 ppm</td>
<td>1 ppm</td>
<td>10 ppm</td>
</tr>
<tr>
<td>N-hexane</td>
<td>500 ppm</td>
<td>50 ppm</td>
<td>50 ppm</td>
</tr>
</tbody>
</table>

In the United States of America, the American Conference of Industrial Governmental Hygienists (ACGIH, 2009) recommends that when exposure to noise and to carbon monoxide, lead, manganese, styrene, toluene, or xylene occurs, then periodic audiometry should be carried out and the results should be carefully reviewed. Also, 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 annual audiometric assessment for workers whose chemical exposure (disregarding the use of respiratory protection) equals 50% of the most stringent criteria for occupational exposure limits, regardless of the noise level.

The Canadian Centre for Occupational Safety and Health (2009) has listed benzene, xylene, ethylbenzene hydrogen cyanide, n-hexane, styrene, trichloroethylene, toluene, among others as chemicals associated with hearing loss.

Organic solvents such as toluene, xylenes, styrene, and trichloroethylene are considered as industrial ototoxic agents under Australian and New Zealand legislation (AS/NZS 1269.0:2005). Also, Australian government bodies such as Safe Work Australia and the Department of Commerce, have recognised solvents as ototoxic agents. Safe Work Australia (2010) indicated that some factors, such as ototoxic chemicals, may interact with noise to produce hearing loss that is greater than that associated with the effects of the individual causes. In addition, the presence of chemicals in the workplace has been suggested as being one of the possible factors leading to the maintained occurrence of noise-induced hearing loss (Safe Work Australia, 2010). In Australia (e.g., Queensland Government, 2004), it has been recommended, until revised standards are established, that the daily noise exposure of workers exposed to solvents be reduced to 80 dBA or below, and that regular audiometric testing should be carried out. Annual audiometry is highly recommended for Australian workers whose airborne exposures for some selected chemicals are at 50% or more of the exposure standards stated in the National Exposure Standards for Atmospheric
Contaminants in the Occupational Environment (NOHSC 1003, 1995), regardless of the noise level.

In Europe, the European Parliament published a noise directive (2003/10/EC), which has been adopted by all member countries since 2006. This directive calls on employers to consider the interaction of noise and work-related ototoxic substances on workers’ health and safety. The European Agency for Safety and Health at Work (2009) has listed solvents such as toluene, styrene, p-xylene, among others as agents with “good evidence” about their adverse effects on hearing. In Germany, a position paper on ototoxic industrial chemicals was issued by the “Noise” and “Hazardous Substances” working groups of the Deutsche Gesetzliche Unfallversicherung (DGUV)’s committee for occupational medicine (Deutsche Gesetzliche Unfallversicherung’s Occupational Medicine Committee, 2006). Among other recommendations, the position paper stated that public risk communication, including all points of contact, should be promoted, and that the ototoxicity of some chemicals should be taken into consideration when specifying occupational exposure limits.

Finally, in Brazil workers can claim compensation for hearing loss induced by occupational exposure to ototoxic chemicals, as a regulation issued in 1999 (Ministério da Previdência e Assistência Social, 1999) recognises the adverse effect of certain chemicals on hearing.

The scenario in most developing nations is very different. In many developing countries legislation is absent or under-enforced and local industrial workplace practices are performed without knowledge of the possible adverse health consequences of chemical agents. In these countries legislation requiring the safe usage of ototoxic chemicals used in industry and agriculture should be enacted, along with the establishment of adequately resourced monitoring agencies (Amedofu & Fuente, 2008).

6. Conclusion

The effects of chemical exposure on the auditory system have been studied by many authors. The findings suggest that chemicals such as solvents, pesticides and metals have both oto-and neuro-toxic properties. Studies conducted in animals have demonstrated that the outer hair cells are affected by solvents. The damage begins in the most external row of cochlear hair cells, and if the exposure continues the damage is spread to the middle and inner row of outer hair cells. A concomitant agent in many industries is noise exposure. Research conducted in animals and humans exposed to solvents and noise have found a synergism between these two agents. The ototoxicity induced by solvents appears to be different than the one induced by noise. Human studies in workers exposed to solvents have shown a higher prevalence of hearing loss among solvent-exposed workers when compared with non-exposed workers.

Additionally studies conducted in human populations exposed to pesticides have shown that these agents are associated with poorer hearing thresholds as well as with poorer performance for some central auditory functioning tests. Research conducted in human subjects exposed to metals such as lead and mercury also indicates that these agents relate to auditory dysfunction.

Current legislation in many countries establishes permissible exposure limits (PELs) for chemicals. These PELs are not based on the possible adverse auditory effects of chemicals.
Therefore, guidelines in some developed countries have emerged to reduce the risk of hearing loss/auditory dysfunction in workers exposed to chemicals alone or to chemicals in combination with noise. There is an urgent need for further studies to establish dose/response relationships. With this information legislation around the world could be modified regarding the PELs for ototoxic agents such as solvents, metals and pesticides.

Health care professionals in the field of audition must be aware of the effects of chemicals on the auditory system and understand the complexity of such effects which relate to ototoxic and neuro-toxic mechanisms. Chemical-exposed workers regardless of their noise exposure level should be routinely monitored with audiological procedures that investigate the peripheral and central auditory system. For these purposes, a test battery approach should be considered. There is still a lack of knowledge of the most sensitive audiological tests for the detection of chemical-induced auditory dysfunction. However, there is evidence that some tests can effectively detect some cases of central auditory dysfunction induced by solvent exposure. Such tests can be also used in populations of workers exposed to other chemicals that are known (or suspected) to have ototoxic properties.

Current industrial processes utilise massive quantities of chemicals that may jeopardise workers’ hearing health. It is the role of audiologists, other hearing health care, and occupational health and safety professionals to prevent chemical-induced hearing loss/auditory dysfunction. To assist prevention, the scientific evidence regarding chemical-induced hearing loss should be disseminated among workers, employers, health care professionals and legislators. Inside factories action to reduce exposure to these agents is essential to decrease the burden of occupational chemical-induced hearing loss. Industry-based initiatives should include the identification of populations at risk, the detection of early signs of chemical-induced hearing loss, and the delivery of hearing conservation programmes to chemical-exposed workers regardless of their noise exposure levels.

7. References


Author by 17 international researchers and research teams, the book provides up-to-date insights on topics in five different research areas related to normal hearing and deafness. Techniques for assessment of hearing and the appropriateness of the Mongolian gerbil as a model for age-dependent hearing loss in humans are presented. Parental attitudes to childhood deafness and role of early intervention for better treatment of hearing loss are also discussed. Comprehensive details are provided on the role of different environmental insults including injuries in causing deafness. Additionally, many genes involved in hearing loss are reviewed and the genetics of recessively inherited moderate to severe and progressive deafness is covered for the first time. The book also details established and evolving therapies for treatment of deafness.

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