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French agency for food, environmental and occupational health & safety

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Occupational co-exposure to noise and chemicals

Summary and conclusions

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COLLECTIVE EXPERT APPRAISAL: SUMMARY AND CONCLUSIONS

regarding the expert appraisal on recommending occupational exposure limits for chemical agents

Reference document on preventing the effects of occupational co-exposure to noise and chemicals

This document summarises and presents the work of the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee)

1- Presentation of the issue

ANSES has been mandated by the French Directorate General for Labour to conduct the expert appraisal work required for setting occupational exposure limit values (OELVs) for a number of substances.
The Agency decided to go ahead and conduct assessments to establish limit values for the substances included in its work programme and methodological work on topics of concern or emerging issues in occupational health, falling within its sphere of competence and the missions assigned to it by its supervisory ministries.

The purpose of this report is therefore to review the knowledge reported in the scientific literature on the effects of chemicals on the auditory system that lead to a decrease in hearing thresholds. When such effects are demonstrated for a substance, they are said to be "ototoxic".

2- Organisation of the expert appraisal

ANSES entrusted examination of this internal request to the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee). This Committee mandated three rapporteurs (one OEL Committee expert, one expert in ototoxicity and one ANSES officer) to conduct this expert work.
The findings of this work led to the drafting of this document, which was discussed by the experts of the OEL Committee on three occasions before being adopted on 9 July 2013. The result of the collective expert appraisal described below takes account of the observations and additional information provided by the Committee members.
This expert appraisal was therefore conducted by a group of experts with complementary skills. It was carried out in accordance with the French Standard NF X 50-110 “Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)”.

3- Description of the method

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The aim of this document is to produce a state-of-the-art review of the literature on the effects on hearing of occupational co-exposure to noise and chemicals.

This document was prepared based on reports from several expert organisations : CONCAWE 2005, WHO 2005, EU-OSHA 2009, IRSST 2009, NEG 2010. Source articles were consulted when it was deemed necessary. In addition, a review of the literature on Medline, Toxline and Scopus was carried out for 2010-2012.

4- Result of the collective expert appraisal

4.1- Identification of the issue

In the assessment of occupational risks, hazard identification involves examining each parameter in isolation to determine its effect on the health of employees. However, most work environments are complex, with exposure to a multitude of physical and chemical agents that are potentially hazardous to health. Despite this, occupational safety criteria are only developed on the basis of results from hazard studies conducted in isolation, and may not be sufficient to protect employees.

Noise is often present in the workplace along with chemical exposure. Consequently, the hearing disorders observed in several occupational categories are mostly attributed to noise exposure alone and do not take into account the possible involvement of other agents. The concept of occupational deafness has often been used as a synonym for hearing loss due to noise, which may not be accurate. Current standards for protection of hearing do not take into account the potential risk posed by chemical exposures.

Before the 1980s, few if any research programmes focused formally on hearing loss induced by chemical compounds. This changed with the publication of reports by groups dedicated to investigating the neurotoxic properties of chemicals (WHO 2005, IRSST 2009, NIOSH 1996, 1998, EU-OSHA 2009, NEG 2010). Since then, considerable progress has been made towards understanding the effects of certain chemicals on the auditory system and their interactions with noise (Chen, 1999; Lataye, 2000, Campo, 1999; Morata, 1989 and 2002), culminating in Directive 89/391/EEC, which, pursuant to Article 6(3), requires employers to give particular attention, when carrying out the risk assessment, '*as far as technically achievable, [to] any effects on workers' health and safety resulting from interactions between noise and work-related ototoxic substances…'*

4.2- Ototoxicity

An ototoxic agent is defined as a chemical that causes a functional impairment, hearing impairment or cell damage in the inner ear, especially to the hair cells, auditory or balance neurons, or the vestibulocochlear nerve.

Substances that impair hearing and balance by acting primarily on the trunk along the central auditory pathways are regarded as neurotoxic. Ototoxicity is systemic toxicity targeting cells involved in auditory function.

Chemical agents responsible for diseases of the ear may be in gaseous (gas, vapour), particle or aerosol form (dust, fumes, mist). Hearing damage results if exposure to these substances occurs at sufficiently high concentrations (which may, however, be lower than those at which the substance is considered toxic in other ways).

The ototoxic action of certain chemicals is heightened by the presence of noise (even at levels, for example, that are lower than those set by legislation as a threshold for initiating preventive action: 80 dBA) and/or by concomitant exposure to other ototoxic substances.

It has long been known that the effects of simultaneous exposure to numerous chemical agents cannot be predicted on the basis of their individual effects (NEG 2010). Often, the effects of exposure to multiple agents exceed the simple addition of the effects produced by single

exposure to each agent (Humes, 1984). Since noise is the commonest exposure causing hearing loss in humans, special attention has been paid to combined exposure to noise and ototoxic agents.

Several studies relating to the ototoxic properties of substances have been conducted with solvents, heavy metals, asphyxiants and certain medicinal products. Studies of combined exposure to different ototoxic substances or simultaneous exposure to ototoxic substances and noise have shown deleterious interactions with respect to hearing. The interactive effects identified were additive or synergistic. According to Calabrese (1991) and Greco et al. (1992), the interactive effects can be defined as follows:

- an additive effect is a phenomenon that occurs when the combined effect of at least two agents is equal to the sum of the effects of each agent considered individually (no direct interaction, 1+1 = 2)
- a synergistic effect refers to an interaction between at least two elements whose combined effect is greater than the sum of their individual effects (effects such as “1+1>2”).

Chemicals with confirmed ototoxic properties, and which are commonly used in the workplace, are listed in the table below.

Class of chemical	Examples
Organic solvents	Styrene, toluene, p-xylene, ethylbenzene, chlorobenzene, trichloroethylene, n-hexane, n-heptane, carbon disulphide
Metals	Lead, mercury, organotins
Asphyxiants	Carbon monoxide, hydrogen cyanide, acrylonitrile, 3,3'-iminodipropionitrile
Other substances	Pesticides (organophosphates, paraquat, pyrethroids, hexachlorobenzene), polychlorinated biphenyls

Table 1: Examples of some substances known for their ototoxicity (NEG 2010)

The different ototoxic agents found in the workplace can damage the auditory function by several different mechanisms. One of the conclusions of the many studies is that hearing loss is sensorineural and that it affects the inner ear via the degeneration of hair cells in the cochlea. One hypothesis is that these cells are affected by the formation of free radicals commonly called reactive oxygen species (ROS) (Chen, 2007; Henderson, 2006). Other chemicals such as metals and pesticides can simultaneously affect the cochlea (Rice, 1997) and the central auditory pathways (Lasky, 1995a; Otto et al., 1993).

Disruption of the membrane structures could be the starting point of cochlear damage. One explanation is the easy penetration of lipophilic solvents in the phospholipid layers, changing the structure and membrane fluidity of the hair cells, which would alter mechanical resistance to movement of the organ of Corti (Campo et al., 1999). This chemical damage leads to the destruction of outer hair cells even after the cessation of exposure, while the inner hair cells appear to be well preserved (Campo et al., 2001; Loquet 2000).

Unlike laboratory animals, humans are characterised by great individual variability in response to noise exposure. As a result, characterising the risks, separating the effects of each agent, and accurately measuring the interactions between agents is a real challenge. Besides noise and exposure to chemicals, certain factors have been identified as influencing the occurrence and degree of hearing loss. These include age, specific exposure during foetal or neonatal development, gender, ethnicity, socioeconomic group, lifestyle and use of medication (Toppila et al., 2000; Ecob et al., 2008).

4.3- Conclusions of the literature review

There is a considerable amount of evidence from the animal studies, using different parameters and tests to show the effects of solvents and asphyxiants on hearing and balance. They enable the following conclusions to be proposed:

- ✓ Chemicals may be ototoxic, causing permanent hearing loss in rats;
- ✓ There are species-dependent differences in the effects on hearing: guinea pigs and chinchillas are much less sensitive than rats. The rat was considered the most appropriate model to assess the risk to humans and it is therefore plausible to transpose the results of experimental studies in rats to humans;
- ✓ It is important to take into account the chemical exposure scenario in the results of publications. Experiments are most commonly performed on animals at rest, so the greater absorption of chemicals by workers when active is not taken into account. Consequently, the identified benchmark doses in animals (NOAEL, LOAEL) are often overestimated;
- ✓ Exposure to solvents produces cochlear damage, as does exposure to noise, but the mechanisms are different. Hearing loss caused by noise occurs through mechanical injury of the stereocilia. However chemicals reach the cochlea usually by damaging the basal region of the cochlea and the third row of outer hair cells. In addition, organic solvents are known to be neurotoxic and as well as cochlear toxicity, are suspected of damaging hearing due to impairment of the central nervous system;
- ✓ The mammalian cochlea is vulnerable to hypoxia induced by chemical asphyxiants. Disruptions in blood supply (ischemia) and the reduction of available oxygen levels (hypoxia) have been suggested as underlying mechanisms responsible for many forms of asphyxiant ototoxicity;
- ✓ Hearing loss at medium frequencies is the most widely reported; the hearing loss increases with the concentration of chemicals, which raises the hypothesis of a dose-dependent relationship;
- ✓ The ototoxic effects of chemicals may continue after cessation of exposure;
- ✓ There is evidence that combined exposure to certain chemicals and noise has a synergistic effect. This can occur when exposure levels are below the exposure limits. There is a critical level at which this synergy occurs but it is difficult to identify.

The overall results from epidemiological studies must be tempered by several uncertainties, of which the main ones are listed below:

- ➢ Assessment of the effects of exposure to a single chemical is especially difficult because employees are typically exposed to mixtures of chemicals whose composition and concentrations vary widely. Few studies have addressed the problem of hearing impairment in people exposed to a specific substance and to noise at about 87 dBA (average noise exposure limit that must never be exceeded);
- ➢ It is well known that a period of at least 14 hours without exposure to noise must precede audiometry to avoid any confusion with the temporary threshold shift (TTS). It might be expected that a period without exposure to a chemical, which would depend on its retention time in the body, is also needed to assess ototoxicity, but this was not clearly demonstrated or implemented in the studies;
- ➢ A major problem in epidemiology is obtaining homogeneous populations. It is essential, but at the same time very difficult, to characterise study populations properly and take into account factors that could affect auditory function, such as age, length of employment, history of exposure to noise or chemicals, diabetes, hypertension, infections, trauma to the ear, the use of ototoxic products (medicinal products, ethanol, tobacco, etc.);
- ➢ In some studies, levels of exposure to chemicals and noise are poorly characterised: only the intervals are provided or only current exposure levels are considered. These studies are inappropriate for determining a NOAEL/LOAEL;
- ➢ Statistical analyses are not always satisfactory: for example, some studies have considered variables with large standard deviations, which implies a non-Gaussian

distribution of the studied population that is not always taken into account in the statistical analysis.

In conclusion, the association between occupational exposure to certain chemicals and impaired auditory function has only recently been suggested: the data are sparse and equivocal. The ototoxicity of these compounds in humans is not well characterised. There are few epidemiological studies to identify the impact of chemicals on hearing. They do however still allow the following consensus conclusions:

- ✓ The ototoxic effect of certain chemicals, especially organic solvents, is highly probable;
- ✓ The hearing loss identified is permanent and the damage may occur both in the peripheral and central nervous systems;
- ✓ Hearing loss can occur at exposure levels close to the 8h-OEL;
- ✓ A dose-response relationship has been identified between the increase in hearing thresholds and levels of exposure to certain chemicals;
- ✓ A synergistic effect of noise and solvent exposure, even at levels below the OEL, was noted for certain substances. In some cases the data confirm that the established 8h-OEL does protect from ototoxicity, which only appears at a much higher concentration level. But sometimes there is nothing to indicate that the selected 8h-OEL can protect from hearing impairment, when associated with noise at around the limit value;
- ✓ A body of information indicates that hearing loss occurs earlier and is higher among employees co-exposed to ototoxic substances and noise compared to those exposed to noise alone;
- ✓ Some experimental data suggest that the effects of some solvents on hearing continue after cessation of exposure. The exposure time required for a chemical to cause hearing loss, with or without co-exposure to noise, has not been characterised. Some researchers believe that people in contact with ototoxic chemicals may begin to present hearing loss two to three years after the start of exposure to these substances, while people exposed to noise would only display similar symptoms after about four to five years;
- ✓ There is great individual variability in the occurrence of hearing loss. It is linked to factors concerning age, gender, genetics, lifestyle (smoking, alcohol, etc.) and health.

5- Recommendations of the OEL Committee:

Considering that:

- ➢ a large number of employees are exposed to chemicals in a noisy environment;
- ➢ hearing loss is one of the most common occupational impairments. It is insidious and painless, and the discomfort it causes has major social consequences;
- ➢ once hearing loss has occurred, the process is irreversible and can continue even after cessation of exposure to the causal chemical agent;
- ➢ there is great individual variability in the susceptibility of employees to incur hearing loss and they are exposed to a wide range of chemicals that could contribute to this loss;
- ➢ preventionists and all the various occupational health professionals are currently not sufficiently aware of the hearing loss associated with exposure to chemicals, unlike that related to noise exposure;
- ➢ European Directive 2003/10/EC on the minimum health and safety requirements regarding the exposure of workers to noise specifies that the employer must take into account – among other things – *when carrying out the risk assessment, any effects on workers' health resulting from interactions between noise and ototoxic substances*;
- ➢ the existing scientific data are insufficient to propose exposure limits that take into account combined exposure to noise and a substance;

The OEL Committee considers it necessary to pay special attention to the effects of co-exposure to chemicals and noise.

The OEL Committee recommends:

- introducing an "ototoxic notation", indicating a risk of hearing impairment in the event of co-exposure to noise and the substance below the recommended OELs, to enable preventionists to implement appropriate measures (collective, individual and/or medical);
- assigning this notation to chemicals for which there is a certain level of evidence on their possible ototoxic effect in the event of co-exposure to noise;
- conducting research to better characterise the risks associated with co-exposure to noise and ototoxic agents;
- conducting further studies to clearly determine the exposure limits, the effects of concentration peaks, the type of medical surveillance to propose, and the intervals between hearing tests required for any substance identified as ototoxic.

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