NOISECHEM: AN EUROPEAN COMMISSION RESEARCH PROJECT ON THE EFFECTS OF EXPOSURE TO NOISE AND INDUSTRIAL CHEMICALS ON HEARING AND BALANCE

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Abstract. Exposure to multiple physical and chemical agents is common in occupational environments but workplace hazards and occupational safety criteria for combined exposures are lacking. NoiseChem is an European Commission research project examining the effects of exposure to noise and chemicals on hearing and balance. Partners in Sweden, Finland, France, Denmark, UK and Poland with expert guidance from partners in the USA will examine workers and study the mechanisms of action in animals to determine the levels of risk associated with joint exposure to noise and solvents. This paper briefly outlines the project details.

Key words: Solvents, Noise, Multiple exposures, Hearing and balance

INTRODUCTION

The effect of combinations of environmental factors on workers’ health requires much attention of researchers as this reflects more closely the work conditions and little is known how individual toxic agents in mixed exposures interact to increase or modify the likelihood of adverse health effects. Most work environments consist of a myriad of physical and chemical agents that are potentially hazardous to health. Study results of isolated workplace hazards are often used to develop occupational safety cri-

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teria that may not be adequate for protecting workers in environments where simultaneous or sequential exposures to a variety of agents occur. Around 30 million people in Europe work in noise environments that are hazardous to hearing, and an additional 10 million work with industrial chemicals considered to be ototoxic, such as solvents, heavy metals and asphyxiants. A considerable number of these workplaces include both industrial chemicals and a noisy environment, thereby, enhancing the risk for hearing loss. The risk from noise exposure is well established, but from exposure to industrial chemicals is less understood. Laboratory studies in animals [1–3] and some occupational exposure studies [4–7] suggest that simultaneous exposures to noise and chemicals produce a hearing loss that is significantly greater than from either agent acting alone. In other words, there is an observed synergistic effect from having combined exposures to noise and chemicals. This means that individual noise and chemicals may be within exposure limits, but in combination they can still pose a risk. If this synergism were confirmed in humans, major changes would be required in the limitations set for occupational hazards to prevent occupational hearing loss. In addition to the synergistic effects on hearing, chemicals may also affect balance and auditory central nervous system function in a way not expected from noise exposure alone. It is important, therefore, to examine the independent and combined effects of chemicals and noise on both the hearing and balance systems of exposed workers. In 1996, the U.S. National Institute for Occupational Safety and Health (NIOSH) developed the National Occupational Research Agenda (NORA) to redefine research priorities based on seven criteria:

- seriousness of the hazard (based on death, injury, disease, disability, and economic impact);
- number of workers affected;
- magnitude of risk, potential for risk reduction;
- expected trend in research area;
- insufficiency of existing research;
- probability that research would make a difference.

NORA identified hearing loss due to noise and chemicals as a priority area. The need for research in this area is further heightened by the lack of occupational guidelines or standards for combined exposures to chemicals and noise.

**OBJECTIVES**

*NoiseChem* proposes to examine study designs, hearing assessment alternatives, and strategies for the analysis of combined effects. Moreover, on the basis of agreed protocols, *NoiseChem*’s goal is to conduct epidemiological studies across eastern and western Europe.

The *NoiseChem* study involves two research groups: (1) those working with animals to determine the mechanisms of ototoxic damage due to noise and chemical interactions through laboratory investigations; and (2) those examining the effects on human audio-vestibular systems using systematic, standardized procedures through epidemiological investigations on factory workers in Sweden, Finland, Poland, and the United Kingdom. A new partner will also be examining workers in France.

There are three work packages (WP) in the program. The objectives are as follows:

- **WP1:** to develop standardized procedures for effective field evaluation of hearing and balance function;
- **WP2:** to determine the effect of exposures to solvents at concentrations commonly found in industry and the interactive effects of solvents and noise on workers’ hearing and balance function;
- **WP3:** to determine the mechanisms in laboratory animals for damage to hearing from solvents and their interaction with noise.

**CURRENT STATUS**

Chemicals, such as toluene, styrene, xylene, trichloroethylene, and carbon disulfide, and their mixtures are commonly used in industry and present a risk to hearing and balance. This risk is exacerbated by noise. Although organic solvents have been used in industry for over 150 years, serious consideration of their ototoxicity began only some 15 years ago. This lack of attention probably derives from the fact that substantial noise is often present in most occupational settings where solvent exposures occur.
and, as a consequence, hearing losses observed in these situations have often been attributed exclusively to noise exposure. Currently, occupational legislation does not consider environmental chemicals hazardous to hearing. Thus, there are many solvent-exposed workers whose needs concerning hearing conservation are unmet.

Recent studies have suggested that the risk to hearing may increase several-fold where the combination of noise and solvents exists. Particularly alarming are the prospects of noise and solvents that, when occurring alone, are within current exposure limits, but when combined, increase synergistically, thus, posing a greater risk to hearing. Therefore, it is important to determine the effects of combined exposures to noise and chemicals for the purposes of hearing conservation and exposure limit standards.

The ototoxicity of environmental agents, such as solvents, metals and asphyxiants, and their interactions with noise are issues just beginning to be addressed internationally; the group of researchers involved in this study have played a significant role in bringing this research to the fore.

Balance dysfunction from solvents has largely been neglected due, in some extent, to the difficulties in testing for it in the field even though both ototoxic and neurotoxic agents can affect balance systems [8,9].

Organic solvents can produce permanent hearing impairment in both people and laboratory animals. The widespread use of these organic solvents and the specific nature of the hearing loss that has been reported pose a significant occupational health risk. Laboratory investigations appear to identify two distinct patterns of cochlear dysfunction and injury following solvent exposure. One pattern produced by toluene involves the impairment of outer hair cells, which normally encode middle frequency tones. These outer hair cells are located in the middle turns. The ototoxicity appears to stem from a preferential perturbation in motility of these cells and, thereby, of sensitivity to sound. Preferential dysmorphia in these cells and impaired regulation of free intracellular calcium levels can occur rapidly and at lower than predicted concentrations of toluene exposure to human brains. Because the outer hair cell alone shows rapid electromotility, a process that is sensitive to $[\text{Ca}^{2+}]$, it may be particularly vulnerable to ototoxic agents that disrupt intracellular calcium regulation. The second pattern produced by trichloroethylene, in contrast to toluene, preferentially impairs inner hair cell-spiral ganglion cell function. It is yet to be determined whether this reflects excitotoxic injury at this synapse.

The NoiseChem study will characterize the development of cochlear impairment to toluene and styrene using repeatedly-within-subject assessment of distortion product otoacoustic emissions and compound action potential. Comprehensive acute cochlear assessment of auditory nerve saturation, cochlear microphonic, and endocochlear potential measures will specify the target cells. Non-ototoxic solvents will be used as controls to identify selective mechanisms of ototoxicity. Toluene preferentially disrupts slow motility in outer hair cells, which encode middle frequency hearing, and elevates intracellular calcium by disrupting intracellular storage and/or release mechanisms. In vitro experiments will identify the specific calcium sequestration mechanism that is impaired by this ototoxic solvent and determine the relationship between changes in outer hair cell morphometry and in outer hair cell and spiral ganglion cell calcium homeostasis.

The mechanisms that favour the interaction of chemicals and noise on auditory function, the possible targets for such effects, and the relationship between neurotoxicants and ototoxicants need to be addressed. While it is possible that any of two agents may have interactive effects, it is not feasible to test all compounds, let alone all combinations of agents. A prominent problem of ototoxicity is that it is not clear which events lead to loss of auditory function.

A major objective of this research is to identify mechanisms by which chemicals disrupt hearing so that accurate predictions of these agents can be made. Once an ototoxicant is recognized, the probability for potentiation of noise-induced hearing loss by the agent must be assessed to allow accurate risk assessment.

Studies on workers in various fields are beginning to show that the combined occupational exposure to solvents and noise can result in greater hearing loss as, for example, in
shipyard painters and paper mill workers, but the detailed exposure and effect relationships have not been identified. In a recent cross-sectional study of workers in a printing plant, the adjusted relative risk estimates for hearing loss were reported as four times greater for the noise group, eleven times greater for the noise and toluene group and five times greater for the solvent mixture group [4,10]. Toluene and noise interactions are clearly indicated. Pure tone audiometric tests alone have been shown to be insufficient for describing the complete effects, as acoustic reflex findings suggest a retrocochlear element to the impairment. Thus, comprehensive evaluations of the peripheral and central auditory nervous system and the auditory efferent pathway are indicated for a complete exposure effects assessment.

Combined exposures to styrene and noise were tested in workers exposed to mixtures of polystyrene resin, methanol, and methyl acetate at concentrations below threshold limit values. The percentage of people lying outside the 90th percentile for the upper limit of hearing was 8.7% for the controls, 12.1% for noise group, and 33.3% for the solvents and noise group [11]. However, these findings were not replicated by another study of workers in a glass-reinforced-plastics industry who were exposed to styrene and noise. No clear relationship was observed between cumulative noise and styrene exposure on audiometric thresholds.

Clear consistency of exposure evaluation and effects assessment are required before studies can be compared.

**NOISECHEM STUDY**

A variety of study designs, which include case reports, case referents, and cross-sectional studies, indicate the multiplicity of objectives in the solvent exposure investigations. A wide variety of metrics and diverse approaches to the measurements of chemical exposures have been used to study auditory effects. These studies are not directly comparable, but provide a clear indication that industrial chemicals affect human hearing and may interact with noise, thus, further exacerbating the situation.

In this study a number of toxicants will be examined, namely – toluene, styrene, xylene, trichloroethylene, carbon disulfide, and solvent mixtures. All of these will be studied with and without simultaneous noise exposure to determine the interaction effects.

These proposed investigations will benefit from the following:
- Detailed individual solvent and noise exposure evaluations.
- Comprehensive study of the peripheral and central auditory and vestibular systems in populations exposed to solvents with and without noise.
- Comprehensive individual risk factors analysis and their impact on effects.
- Identification of possible susceptibility factors and individuals at most risk.
- Large-scale, multi-centre European study of a range of solvents with and without noise and tested using a unified agreed set of protocols.
- Hazard and risk assessments for the combinations of solvents and noise.
- Detailed dose and response relationships for toluene, styrene, xylene, trichloroethylene, carbon disulfide and a combination of solvents with and without noise.
- Estimation of solvent exposure variation across Europe.
- Real-life mixed solvent exposure assessments and their effects on the hearing and balance systems. Balance effects have largely been neglected, but need to be investigated for both ototoxic and neurotoxic agents.
- Detailed investigation of balance disturbances from exposures to a large number of solvents, this being the first.

The implications of solvent ototoxicity to occupational health and especially hearing conservation are far reaching. Ultimately, they can be expected to widen the framework for analyses of the relationship between auditory function and working conditions. They may encourage a paradigm shift in hearing conservation, refocusing attention away from noise to hearing.

The following areas will be addressed by this group as the study progresses:
Appropriateness of the current threshold limits when certain hazards occur simultaneously in the workplace.

The adequacy of current hearing assessment and protection strategies.

Role of hearing assessment as applied to the early identification of those most susceptible to neurotoxic disorders.

Method for general risk assessment of interaction between two or more toxic agents, as such exposures are common in a majority of occupational settings.

Models for general risk assessment concerning interactions between chemicals and noise, which has never been proposed before now.

Further data on outcomes following specific exposure combinations as a basis for the generation of hypotheses concerning mechanisms that cause potentiation of auditory disorders.

Development of methods to estimate risks of common occupational exposures.

One of the main study objectives is to improve our understanding of the health risks of workers exposed to a mixture of solvents or combination of solvents and noise and, thereby, to reduce the harmful effects. Cooperation amongst the European noise specialists, engaged in research in their own countries, will be achieved by their coming together and jointly gaining from each other's experiences to improve the state of the art in industrial chemicals and noise-related effects research. The work plan is summarized in Fig. 1, which sets out the environ-

<table>
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<th>Chemicals to be studied</th>
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<th>Biomonitoring</th>
<th>Health effects</th>
<th>Audio-vestibular findings</th>
<th>NoiseChem</th>
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<tr>
<td>Toluene</td>
<td>Glues, paints: many industrial processes</td>
<td>Hippuric acid in urine</td>
<td>Cognitive and neurological dysfunction, dizziness, hearing loss</td>
<td>Altered auditory brainstem responses, relative risk to hearing x5 for toluene and x11 for toluene and noise in workers</td>
<td>NoiseChem proposes a systematic and thorough investigation across a number of industries</td>
</tr>
<tr>
<td>Xylene</td>
<td>Paints, degreasers, solvents for resins, gum and rubber. Medical and industrial applications</td>
<td>Methylhippuric acid in urine</td>
<td>Decreased peripheral nerve function, CNS symptoms</td>
<td>Reduced auditory sensitivity</td>
<td>- Assessment with unified and appropriate test procedures</td>
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<td>Styrene</td>
<td>Plastics, latex paints and coatings, polyesters, synthetic rubber. Wide use in packaging industry</td>
<td>Mandelic acid and PGA in urine</td>
<td>Changes in cerebral activities, dizziness, hearing loss, hepatotoxic</td>
<td>Cortical responses affected, vestibular disturbances, slight hearing changes reported, % outside upper limit of hearing were 12% for noise and 33% for noise and styrene</td>
<td>- Assessment of dose/response data</td>
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<td>Trichloroethylene</td>
<td>Metal degreaser, manufacture of adhesives, paints, pesticides, paint strippers, varnishes, cleaning fluids</td>
<td>Trichloroacetic acid and trichloroethanol in urine</td>
<td>Headache, loss of memory, neural conduction deficits, hepatotoxic, hearing loss</td>
<td>Mid-high frequency hearing loss and ABR abnormalities, vestibular system also affected</td>
<td>- Assessment of type and degree of interaction with noise</td>
</tr>
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<td>Carbon disulfide</td>
<td>Pesticide, fumigant, manufacture of viscose-rayon, vulcanization of rubber</td>
<td>2-thiothiazolidine-4-carboxylic acid (TTCA) in urine</td>
<td>Extensive neurological deficits, imbalance and hearing loss</td>
<td>Delayed ABR, high frequency hearing loss, synergistic action with noise</td>
<td>- Quantification of risks to hearing and balance systems</td>
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<tr>
<td>Solvent mixtures</td>
<td>Common in many industrial applications</td>
<td>Test for main component in urine</td>
<td>Neurotoxicity</td>
<td>Impaired interrupted speech discrimination, cortical response abnormalities</td>
<td>- Alter hearing conservation strategies to safeguard the hearing and balance function of millions of workers across Europe.</td>
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<tr>
<td>Solvent and noise</td>
<td>Industrial plants with noisy machinery and solvent use</td>
<td>Test for solvent in urine and noise exposure</td>
<td>Hearing loss and specific solvent effects</td>
<td>Synergistic effect on hearing in shipyard workers, paper mills, printers, rayon manufacturers</td>
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mental and health aspects to be studied in humans and animals, together with the objectives to be achieved, and the deliverables. Table 1 provides the details of the chemicals to be studied, their usual applications in industry, and their monitoring in relation to NoiseChem targets. Noise is a well-recognised hazard to hearing, but chemicals in the workplace and in the environment generally also pose a great hazard to hearing and particularly balance, yet most people remain unaware of this possibility. Chemical exposure, which evokes dizziness and imbalance can be disabling and leads the individual to be socially isolated. The social objective of NoiseChem project is to provide workers with the information on hazards of chemicals so that they can make informed choices and furthermore to allow decision makers to be armed with the most relevant scientific information to make appropriate decisions with regard to public health policy on chemical exposures, particularly mixed exposures.

REFERENCES

Fig. 1. NoiseChem – the work plan.


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